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A multicenter, postmarketing surveillance of elobixibat in patients with chronic constipation in Japan: A final analysis report

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Abstract

Objective: An interim analysis of postmarketing surveillance reported the safety and efficacy of elobixibat, a laxative medication that inhibits the ileal bile acid transporter, at 4 weeks in approximately 1000 patients with chronic constipation in Japan. However, its long-term safety and efficacy in elderly patients remain unclear. This study aimed to conclude and report the final analysis of postmarketing surveillance, including 52-week safety and efficacy profiles in a clinical practice setting, using approximately 3000 patients.

Methods: The overall survey period spanned from June 2018 to May 2022. Observation periods were set at 4 weeks (4-week treatment period) and 52 weeks (52-week treatment period). Adverse drug reactions and efficacy outcomes, including defecation frequency, Bristol Stool Form Scale scores, and patient satisfaction, were analyzed.

Results: The 4-week safety analysis set included 3638 patients with a mean age of 70.8 years, and 73.7% were aged ⩾65 years. Most patients (62.5%) were treated with elobixibat alone, while the rest received concomitant laxatives. In total, 231 patients (6.35%) experienced adverse drug reactions, with gastrointestinal disorders (6.02%) such as diarrhea (3.35%) and abdominal pain (2.06%), being the most common adverse drug reaction. The adverse drug reaction incidence in elderly patients aged ⩾65, ⩾75, and ⩾85 years was 5.49%, 4.85%, and 2.80%, respectively. In the 52-week treatment period, adverse drug reaction incidence was 5.40% (71/1315 patients), similar to that in the 4-week treatment period. Regarding efficacy, defecation frequency and Bristol Stool Form Scale scores significantly improved from week 2 onward, regardless of the age group and administration timing (before breakfast, lunch, or dinner). Most patients reported satisfaction from week 2 onward (6.0%, 66.9%, 78.6%, and 90.4% at baseline, weeks 2, 4, and 52, respectively).

Conclusion: This study confirmed the long-term safety and efficacy of elobixibat in patients with chronic constipation, including many elderly ones, in routine clinical practice.

Keywords

Elobixibat, postmarketing surveillance, chronic constipation, long term, safety, efficacy

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Introduction

Chronic constipation (CC) is a persistent condition that significantly impacts the quality of life of individuals, affecting their school work, work, and sleep.[1,2] CC prevalence increases with age in both genders, particularly among individuals aged 60 and older,[3] with notable prevalence in Japanese adults aged 65 years and above.[4,5]

Elobixibat hydrate, a selective ileal bile acid transporter inhibitor, increases the concentration of bile acid entering the colon, promoting bowel movements by stimulating colonic secretion and motility.[6–9] A phase 3 study showed that oral administration of 10 mg elobixibat once daily before breakfast was effective for CC and generally well-tolerated. The

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most common adverse drug reactions (ADRs) were abdominal pain and diarrhea. Elobixibat also demonstrated good tolerability in a 1-year treatment study.[10] Based on these clinical results, elobixibat was approved for CC treatment, except for nonfunctional constipation, in Japan in January 2018. However, these phase 3 studies involved a small sample size (approximately 500 patients total). The mean age of patients with CC was 43 years, with 83% being female.[10] Although subsequent Japanese studies have been conducted, the long-term safety and efficacy of elobixibat in older patients remain unclear.[11,12] For instance, elobixibat may slightly reduce plasma low-density lipoprotein (LDL) cholesterol levels[10,13] due to its mechanism of action.[7] However, it is necessary to investigate whether LDL cholesterol changes develop into an ADR in elderly patients with poor nutrition. To evaluate the postmarketing safety and efficacy of elobixibat in patients, especially long-term safety and efficacy in elderly patients in clinical practice, we conducted a surveillance postmarketing study with over 3000 patients, including many elderly patients, in Japan over 4 years. We previously reported an interim analysis of this study at 4 weeks of treatment for approximately 1000 patients, without including 52-week treatment data.[14] As the surveillance has concluded, we now report the results of the final analysis of the drug's safety and efficacy at 4 and 52 weeks.

Methods

Patients and surveillance design

This prospective, multicenter, postmarketing survey assessed the safety and efficacy of elobixibat in patients with CC. The overall study period was planned from June 2018 to December 2022, aiming to enroll 3000 patients by December 2021. The observation period was set at 4 weeks (4-week treatment period) and 52 weeks (52-week treatment period), with the latter applying only to patients who continued treatment beyond the initial 4-week period.

The sample size rationale was as follows. Based on the number of patients in Japanese phase 2 and 3 studies,[10,13] ADRs occurring at a frequency of 1% were detected with 95% power. However, to evaluate elobixibat safety in real-world clinical settings, a sample size of 3000 patients was deemed necessary to detect ADRs occurring at a 0.1% rate with 95% power. Given the long-term use of elobixibat, a sample size of 300 patients was deemed necessary to detect ADRs occurring at a 1% rate with 95% power. Based on the >70% continuation rate of elobixibat in the Japanese long-term study,[10] it was expected that many patients would transition to the 52-week treatment study, making the enrollment of 300 patients from a pool of 3000 feasible. Therefore, the sample size was set at 3000 for the 4-week treatment and >300 for the 52-week treatment.

No selection or exclusion criteria were set, and patients with CC who received elobixibat for the first time were enrolled, encompassing 600 institutions across Japan. CC was diagnosed according to the Japanese clinical guidelines for CC.[15] Elobixibat hydrate (GOOFICE® Tablets, EA Pharma Co., Ltd., Tokyo, Japan) was prescribed and administered as per the product label.[16] According to the "Dosage and Administration" of elobixibat, a 10-mg oral dose was given once daily before a meal, and the dose was adjusted to 5 or 15 mg based on disease severity and adverse events. Patient baseline characteristics, medication records, adverse events, and efficacy assessments were collected using an electronic case report form (CRF).

This survey was conducted in accordance with the Declaration of Helsinki and the Ministry Ordinance on Good Post-Marketing Study Practice issued by the Japanese Ministry of Health, Labor, and Welfare, which waived the need for ethical approval, including both written and informed consent, as well as institutional review board approval. However, informed consent was obtained verbally from all participants before study enrollment. The study protocol was reviewed and approved by the Pharmaceuticals and Medical Devices Agency prior to study initiation. This study was registered with the Japan Registry of Clinical Trials (jRCT1080223950).

Safety assessments

ADRs were defined as adverse events for which a causal relationship with elobixibat could not be ruled out. The causal relationship between the drug and adverse events, as well as their seriousness, was assessed by investigators at each facility. ADRs were classified according to the Medical Dictionary for Regulatory Activities version 25.1. If the same event occurred multiple times in the same patient during the same observation period or subperiod, only the first occurrence was counted. The incidence of ADRs in the overall population and in subgroups aged ⩾65, ⩾75, and ⩾85 years was calculated for the 4- and 52-week treatment periods. ADRs occurring up to the day of discontinuation or termination of elobixibat therapy were included in the incidence rate calculation.

Efficacy assessments

Efficacy data were collected through patient interviews by physicians using questionnaires (Supplemental material 1) at baseline and at weeks 2, 4, 12, 24, 36, and 52 after initial treatment. Efficacy outcomes included weekly defecation frequency, Bristol Stool Form Scale (BSFS) scores, patient satisfaction with bowel movements, bloating, straining during defecation, presence or absence of fecal disimpaction, and time to most recent defecation (hours) after elobixibat administration (hereafter referred to as time to defecation). Weekly defecation frequency was defined as the number of defecations in the week prior to each observation time point.

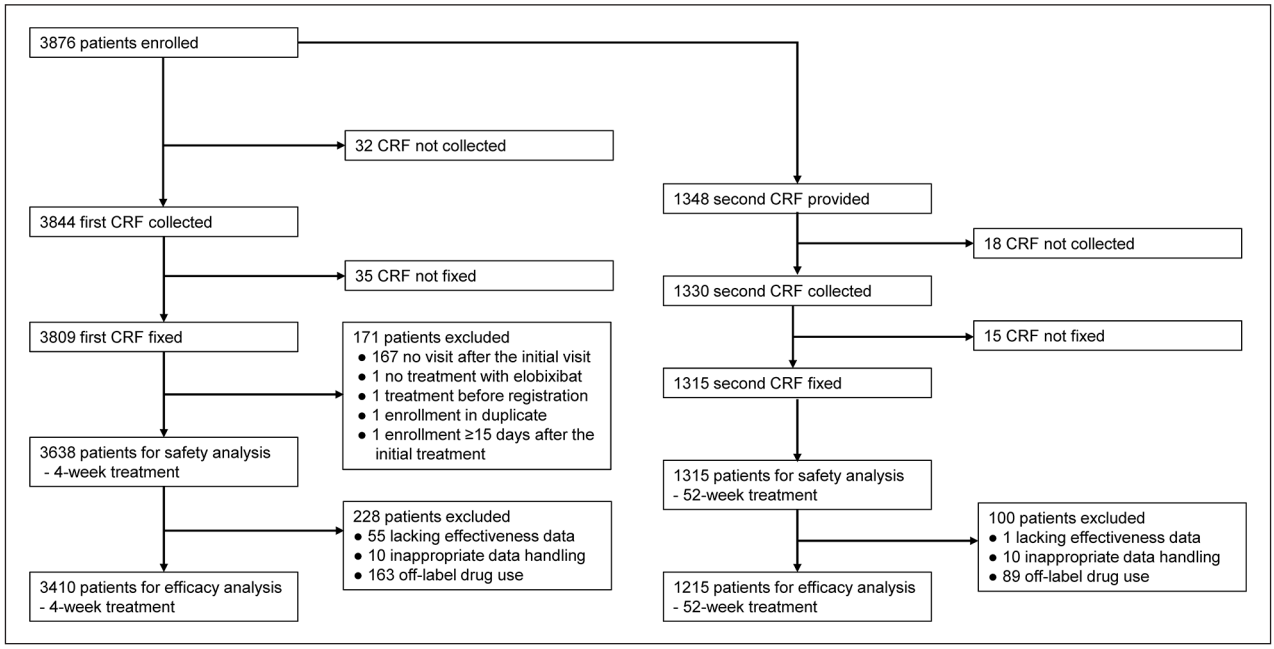

Figure 1. Patient disposition.

In a subgroup analysis, the effects of advanced age and timing of elobixibat administration on safety and/or efficacy outcomes were also evaluated.

Statistics

Demographic and disease characteristics at baseline were summarized using descriptive statistics. The safety analysis set comprised all patients who received the study drug and had safety information, excluding those previously treated with elobixibat at the time of study enrollment. The efficacy analysis set excludes patients without efficacy data.

ADR incidences between subgroups were compared using Fisher's exact test. Defecation frequency, BSFS score, and presence or absence of fecal disimpaction were compared pairwise between baseline and each observation time point using paired *t*-test, Wilcoxon test, and McNemar's test, respectively. The correlations of time to defecation between observation time points were examined using Pearson's product–moment correlation coefficient (r). The consistency of time to defecation across multiple observation time points for the same patients was assessed using the intraclass correlation coefficient (ICC) model 1, k. The cumulative proportion of patients who discontinued combination therapy with other laxatives was plotted using the Kaplan–Meier method. Discontinuation of combination therapy was defined as the first discontinuation of all such drugs. Patients who discontinued or terminated elobixibat therapy were censored at their last observation. The significance level was set at 5% (two-tailed). Statistical analyses were performed using SAS 9.4 (SAS Institute Japan Ltd, Tokyo, Japan).

Results

Patient disposition and demographics

The overall survey period spanned from June 2018 to May 2022. A total of 3876 patients with CC were enrolled across 682 study sites, and 3809 initial CRFs for the 4-week observation period were completed (Figure 1). After the exclusion of patients, 3638 and 3410 patients were included in the safety and efficacy analysis sets, respectively, for the 4-week treatment. Of the patients who completed the 4-week treatment and continued therapy, a total of 1315 and 1215 patients were included in the safety and efficacy analysis sets, respectively, for the 52-week treatment (Figure 1).

Baseline patient characteristics in the 4- and 52-week safety analysis sets are shown in Table 1. In the 4-week treatment, among 3638 patients, 61.1% were female. The mean (SD) age was 70.8 (16.4) years; 73.7% were aged ⩾65 years, 51.6% were aged ⩾75 years, 18.6% were aged ⩾85 years, and 0.2% were aged <15 years. Among the 3638 patients, 47.3% had a disease duration of ⩾5 years and 10.3% had IBS-C. Most patients (62.8%) had been treated with other prescription laxatives for constipation within 1 month before starting elobixibat administration. The main laxatives were saline laxatives (54.8%) and stimulant laxatives (39.9%). Overall, most patients (62.5%) were treated with elobixibat alone, while the rest (37.5%) received concomitant laxatives, including saline laxatives (52.8%) and stimulant laxatives (33.7%). Baseline characteristics for the 52-week treatment were similar to those for the 4-week treatment.

Table 1. Baseline characteristics of patients in the safety analysis set for 4- and 52-week treatments.

Characteristic	4-week treatment		52-week treatment	
	(*N* = 3638)		(*N* = 1315)	
	n	%	*n*	%
Sex				
Male	1414	38.9	535	40.7
Female	2224	61.1	780	59.3
Age (years)				
Mean ± SD	70.8	±16.4	71.7	±16.3
<15	7	0.2	4	0.3
⩾65	2680	73.7	991	75.4
⩾75	1878	51.6	716	54.4
⩾85	678	18.6	270	20.5
BMI (kg/m^2)				
<18.5	275	7.6	101	7.7
18.5–25	1511	41.5	535	40.7
⩾25	553	15.2	196	14.9
Outpatient/inpatient				
Outpatient	3296	90.6	1151	87.5
Inpatient	342	9.4	164	12.5
Disease duration of CC (years)				
<5	1404	38.6	481	36.6
⩾5	1719	47.3	613	46.6
IBS-C				
Yes	374	10.3	137	10.4
Main comorbidity				
Diabetes mellitus	610	22.3	212	20.7
Renal dysfunction	219	8.0	72	7.0
Liver dysfunction	111	4.1	32	3.1
Biliary system disease	59	2.2	15	1.5
Parkinson's disease	81	3.0	42	4.1
Depression	129	4.7	55	5.4
GERD	539	19.7	179	17.5
Prior OTC laxatives				
Yes	321	8.8	104	7.9
Prior prescribed laxatives				
Yes	2286	62.8	851	64.7
Specific prior prescribed laxatives				
Saline laxatives	1252	54.8[a]	463	54.4[a]
Sugar-like laxatives	24	1.0[a]	4	0.5[a]
PEG preparations	72	3.1[a]	9	1.1[a]
Intestinal secretagogues	429	18.8[a]	168	19.7[a]
Bulk-forming laxatives	42	1.8[a]	14	1.6[a]
Stimulant laxatives	911	39.9[a]	388	45.6[a]
Others	526	23.0[a]	197	23.1[a]
Concomitant use of laxatives				
Yes	1364	37.5	567	43.1[b]
Specific concomitant laxatives[b]				
Saline laxatives	720	52.8[b]	305	53.8[b]
Sugar-like laxatives	13	1.0[b]	4	0.7[b]
PEG preparations	39	2.9[b]	35	6.2[b]
Intestinal secretagogues	157	11.5[b]	91	16.0[b]
Bulk-forming laxatives	28	2.1[b]	10	1.8[b]
Stimulant laxatives	459	33.7[b]	214	37.7[b]
Others	413	30.3[b]	175	30.9[b]

BMI: body mass index; CC: chronic constipation; IBS-C: irritable bowel syndrome with constipation; GERD: gastroesophageal reflux disease; OTC: over-the-counter; PEG: polyethylene glycol.

[a]The proportion of specific laxatives is presented as a percentage of all who used any prescribed laxative.

[b]The proportion of specific laxatives is presented as a percentage of all the patients who concomitantly used any laxative.

Table 2. Drug dosage and continuation status in the safety analysis set.

Drug dosage and continuation status	4-week treatment (*N* = 3638)		52-week treatment (*N* = 1315)	
	n	(%)	*n*	(%)
Maximum daily dose				
1 tablet (5 mg)	485	(13.3)	172	(13.2)
2 tablets (10 mg)	2829	(77.8)	942	(71.6)
3 tablets (15 mg)	321	(8.8)	194	(14.8)
Others	3	(0.1)	6	(0.5)
Medication continuation				
Continued	2765	(76.0)	728	(55.4)
Discontinued or terminated	873	(24.0)	587	(44.6)
Reasons for discontinuation or termination				
Symptom improvement	170	(4.7)	190	(14.4)
Lack of efficacy	225	(6.2)	89	(6.8)
AEs	154	(4.2)	50	(3.8)
Patient request (not AEs)	177	(4.9)	103	(7.8)
Getting pregnancy	0	(0.0)	1	(0.1)
No visits after the first visit	0	(0.0)	—	
No visits after the middle of treatment period	124	(3.4)	144	(11.0)
Others	23	(0.6)	10	(0.8)
Administration timing[a]				
Before breakfast	1978	(67.4)	518	(71.3)
Before lunch	147	(5.0)	40	(5.5)
Before dinner	683	(23.3)	138	(19.0)
Others	128	(4.4)	31	(4.3)

AEs: adverse events.
[a]The proportion of administration timing in week 4 of the 4-week treatment period (total valid responders = 2936) and in week 52 of the 52-week treatment period (total valid responders = 727).

Dose and continuation status

For the safety analysis set of the 4-week and 52-week treatment periods, most patients took elobixibat daily dose of two tablets (10 mg) and continued elobixibat treatment for more than 4 weeks (Table 2). The continuation rate of elobixibat was 76.0% and 55.4% at the end of the 4-week and 52-week treatment periods, respectively. The main reasons for treatment discontinuation or termination were symptom improvement, lack of efficacy, patient requests, and adverse events (Table 2).

Regarding administration timing, most patients took elobixibat before breakfast, followed by dinner, regardless of the length of the treatment period (Table 2).

Overall safety

Of the 3638 patients in the 4-week treatment safety analysis set, 231 (6.35%) experienced ADRs (Table 3). The ADRs (⩾4 patients (>0.10%)) were gastrointestinal disorders (6.02%), including diarrhea (3.35%), abdominal pain (2.06%), nausea (0.30%), constipation (0.19%), bloating (0.14%), feces soft (0.14%), and frequent bowel movements (0.11%). Unexpected ADRs were eructation, dyschezia, feeling abnormal, death, and fall (0.03% each). There was only one case (0.03%) of serious ADR, which was death in an 82-year-old female patient with a medical history of aortic aneurysm, angina pectoris, and Alzheimer's disease. She died 3 days after enrollment; however, the cause of death and information about elobixibat were not provided. All other ADRs were non-serious, and most had been resolved or were recovering.

In the 52-week safety analysis set, the incidence of ADRs was 5.40% (71/1315 patients), slightly lower than that in the 4-week treatment (Table 3). Of the patients with ADRs, 41 reported ADRs within 4 weeks of treatment initiation. The ADRs (⩾2 patients (>0.10%)) were gastrointestinal disorders (4.79%), including diarrhea (2.89%), abdominal pain (1.22%), constipation (0.46%), nausea (0.15%), and bloating (0.15%), decreased appetite (0.23%), as well as hypertension (0.23%). Unexpected ADRs were hypertension (0.23%), nasopharyngitis, cardiac failure, cough variant asthma, gastrointestinal hypermotility, deep vein thrombosis, and chronic gastritis (0.08% each). No serious ADRs were reported.

Table 3. Adverse drug reactions (ADRs) during the 4-week and 52-week treatment periods.

ADRs	4-week treatment								52-week treatment							
	Total		⩾65 years		⩾75 years		⩾85 years		Total		⩾65 years		⩾75 years		⩾85 years	
All the patients	3638		2680		1878		678		1315		991		716		270	
Any ADR	231	(6.35)	147	(5.49)	91	(4.85)	19	(2.80)	71[a]	(5.40)	54	(5.45)	36	(5.03)	13	(4.81)
Nasopharyngitis	0		0		0		0		1	(0.08)	1	(0.10)	0		0	
Decreased appetite	3	(0.08)	2	(0.07)	1	(0.05)	0		3	(0.23)	2	(0.20)	1	(0.14)	0	
Headache	1	(0.03)	1	(0.04)	1	(0.05)	0		0		0		0		0	
Cardiac failure	0		0		0		0		1	(0.08)	1	(0.10)	1	(0.14)	1	(0.37)
Hypertension	0		0		0		0		3	(0.23)	3	(0.30)	2	(0.28)	1	(0.37)
Deep vein thrombosis	0		0		0		0		1	(0.08	1	(0.10)	1	(0.14)	0	
Hot flush	1	(0.03)	1	(0.04)	0		0		0		0		0		0	
Cough variant asthma	0		0		0		0		1	(0.08)	1	(0.10)	0		0	
Gastrointestinal disorders	219	(6.02)	137	(5.11)	83	(4.42)	19	(2.80)	63	(4.79)	47	(4.74)	31	(4.33)	11	(4.07)
Abdominal discomfort	3	(0.08)	1	(0.04)	1	(0.05)	1	(0.15)	1	(0.08)	1	(0.10)	1	(0.14)	1	(0.37)
Abdominal pain	75	(2.06)	43	(1.60)	22	(1.17)	1	(0.15)	16	(1.22)	11	(1.11)	6	(0.84)	0	
Abdominal pain lower	1	(0.03)	0		0		0		0		0		0		0	
Abdominal pain upper	0		0		0		0		1	(0.08)	0		0		0	
Anal incontinence	1	(0.03)	1	(0.04)	1	(0.05)	0		1	(0.08)	1	(0.10)	1	(0.14)	0	
Bloating	5	(0.14)	2	(0.07)	2	(0.11)	0		2	(0.15)	2	(0.20)	1	(0.14)	0	
Chronic gastritis	0		0		0		0		1	(0.08	1	(0.10)	1	(0.14)	1	(0.37)
Colitis ischemic	1	(0.03)	0		0		0		0		0		0		0	
Constipation	7	(0.19)	4	(0.15)	1	(0.05)	1	(0.15)	6	(0.46)	6	(0.61)	4	(0.56)	3	(1.11)
Diarrhea	122	(3.35)	85	(3.17)	53	(2.82)	15	(2.21)	38	(2.89)	29	(2.93)	19	(2.65)	6	(2.22)
Dyschezia	1	(0.03)	1	(0.04)	1	(0.05)	0		0		0		0		0	
Eructation	1	(0.03)	0		0		0		0		0		0		0	
Feces discolored	2	(0.05)	0		0		0		0		0		0		0	
Feces soft	5	(0.14)	4	(0.15)	3	(0.16)	1	(0.15)	1	(0.08)	1	(0.10)	1	(0.14)	0	
Flatulence	0		0		0		0		1	(0.08)	1	(0.10)	0		0	
Frequent bowel movements	4	(0.11)	3	(0.11)	2	(0.11)	0		1	(0.08)	1	(0.10)	1	(0.14)	0	
Gastrointestinal hypermotility	0		0		0		0		1	(0.08)	0		0		0	
Nausea	11	(0.30)	6	(0.22)	6	(0.32)	0		2	(0.15)	1	(0.10)	1	(0.14)	0	
Vomiting	3	(0.08)	3	(0.11)	2	(0.11)	0		0		0		0		0	
Hepatic function abnormal	0		0		0		0		1	(0.08)	1	(0.10)	1	(0.14)	1	(0.37)
Liver disorder	1	(0.03)	1	(0.04)	0		0		1	(0.08)	1	(0.10)	0		0	
Rash	3	(0.08)	2	(0.07)	2	(0.11)	0		0		0		0		0	
Urticaria	1	(0.03)	1	(0.04)	1	(0.05)	0		0		0		0		0	
Death	1	(0.03)	1	(0.04)	1	(0.05)	0		0		0		0		0	
Feeling abnormal	1	(0.03)	1	(0.04)	1	(0.05)	0		0		0		0		0	
Fall	1	(0.03)	1	(0.04)	1	(0.05)	0		0		0		0		0	

Values are *n* (%).

[a]Including 41 patients who had experienced ADRs during the 4-week treatment period.

The incidence of ADRs by subperiod of the 52-week treatment gradually decreased: 2.51% (33/1315 patients) from initial treatment to week 4, 2.06% (27/1309 patients) from week 5 to 24, and 1.75% (16/914 patients) from week 25 to 52. A similar reduction in incidence was observed for diarrhea (1.60%, 0.92%, and 0.66%, respectively) and abdominal pain (0.76%, 0.31%, and 0.11%, respectively).

Safety in older patients

In the 4-week treatment safety analysis set, the incidence of ADRs in older patients aged ⩾65, ⩾75, and ⩾85 years was low with age, being 5.49%, 4.85%, and 2.80%, respectively (Table 3). Furthermore, the incidence of ADRs in patients aged ⩾65, ⩾75, and ⩾85 years with a BMI of $<18.5\,kg/m^2$ was 7.98% (15/188 patients), 5.11% (7/137 patients), and 2.04% (1/49 patients). ADRs related to weight loss or decreased LDL cholesterol were not reported across all older age groups.

In the 52-week treatment safety analysis set, the incidence of ADRs in individuals aged ⩾65, ⩾75, and ⩾85 years was 5.45%, 5.03%, and 4.81%, respectively (Table 3).

Efficacy

Defecation frequency

The mean (standard deviation (SD)) weekly defecation frequency significantly increased from baseline shortly after treatment initiation (5.4 (2.6) at week 4 versus 2.9 (2.4) at

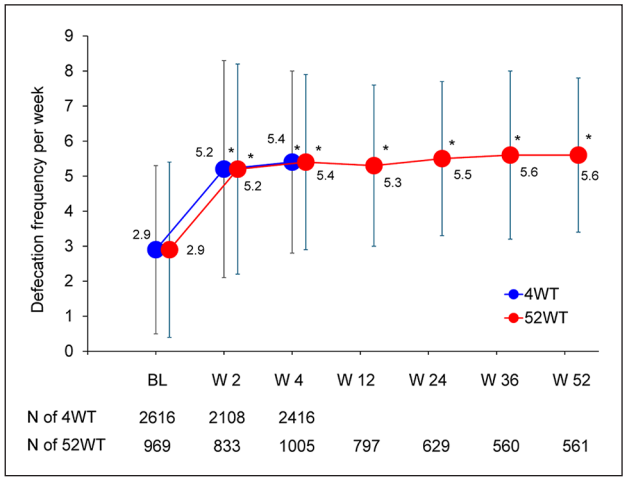

Figure 2. Time course of defecation frequency per week in 4-week treatment (4WT) and 52-week treatment (52WT) in the overall population (all age groups). Mean ± standard deviation.
BL: baseline; *N*: number.
*$p < 0.0001$ versus baseline.

baseline, $p < 0.0001$ for 4-week treatment) and remained stable over 52 weeks (5.6 (2.2) at week 52 versus 2.9 (2.5) at baseline, $p < 0.0001$ for 52-week treatment) (Figure 2).

BSFS score

Most patients had a baseline BSFS score of ⩽3 (mean (SD), 2.3 (1.3), $n = 3064$). The score shifted toward the ideal stool score of 4 at weeks 2 and 4 (Figure 3) and was significantly different from that at baseline at the 4-week observation (mean (SD), 3.8 (1.3), $n = 2289$, $p < 0.0001$, and 3.9 (1.1), $n = 2700$, $p < 0.0001$, respectively). This improvement was also observed at week 52 (3.9 (0.8), $n = 637$, $p < 0.0001$ vs 2.3 (1.4), $n = 1087$ at baseline) (Figure 3).

Patient satisfaction

Few patients were satisfied with baseline conditions (satisfied and slightly satisfied: 6.0%) in the 4-week treatment. However, most patients became satisfied by week 2 or later (66.9% and 78.6% at weeks 2 and 4, respectively). This trend was also observed in the 52-week treatment (Figure 4).

Similar improvements in defecation frequency (Supplemental material 2, Figure S1(a)–(c)), BSFS score (Supplemental material 2, Figure S2(a)–(c)), and patient satisfaction (Supplemental material 2, Figure S3(a)–(c)) were observed across elderly patients aged ⩾65, ⩾75, and ⩾85 years.

Other efficacy outcomes

Table 4 summarizes additional efficacy outcomes. While the proportion of patients frequently or always experiencing bloating was high at baseline (38.2%), it gradually decreased at week 2 (9.5%) and week 4 (5.4%), remaining low through week 52 (2.3%). A similar trend was observed for straining during defecation. The proportion of patients requiring fecal disimpaction during defecations decreased significantly by week 2 and thereafter.

Time from elobixibat administration to defecation

The mean time to defecation after elobixibat administration was approximately 6 h, with over 80% of patients defecating within 24 h. The time to defecation was constant over 52 weeks (Table 4). The proportion of patients who responded that they had not yet defecated within 24 h after taking elobixibat gradually decreased with an increase in the duration of elobixibat administration. During the 52-week treatment period, some degree of correlation was found in the time to defecation across the observation points ($r = 0.30$–0.94, $p < 0.0001$ for all) (Supplemental material 2, Figure S4). Furthermore, the ICC [1, 6] for time to defecation using all six observation time points from weeks 2 to 52 was high, exceeding 0.88 (Table 5), indicating that bowel movements typically occurred at a consistent time for each patient.

Effects of administration timing on efficacy

The proportions of patients taking elobixibat at different times (i.e., before breakfast, lunch, or dinner) were similar between baseline and week 4 or week 52 (Table 6). Defecation parameters, including weekly defecation frequency and BSFS score, showed significant and comparable improvements regardless of administration time. Patient satisfaction followed the same pattern (Table 6).

The mean time to defecation following elobixibat administration before breakfast was short compared with that following administration before dinner (Table 6). To address this time difference, a distribution of times to defecation was prepared using data from the 4-week and 52-week treatment periods. The most frequent time to defecation following drug administration before breakfast was 3–5 h at both weeks 4 and 52. In contrast, two peaks at 6–8 h and 12–14 h were observed with the administration before dinner at weeks 4 and 52 (Figure 5(a) and (b)).

Monotherapy and combination therapy

In the efficacy analysis set of 3410 patients, 2125 had a history of prior prescribed laxative use. Of these, 1026 (48.3%) switched to elobixibat monotherapy at the start of elobixibat treatment (Table 7). A similar switching was observed over the 52-week treatment period. Meanwhile, for 1177 patients who received elobixibat in combination with other laxatives at the start of elobixibat treatment, the Kaplan–Meier plot showed a gradual increase in withdrawal from combination therapy up to around 30 weeks (11.15% at 30 weeks) (Figure 6).

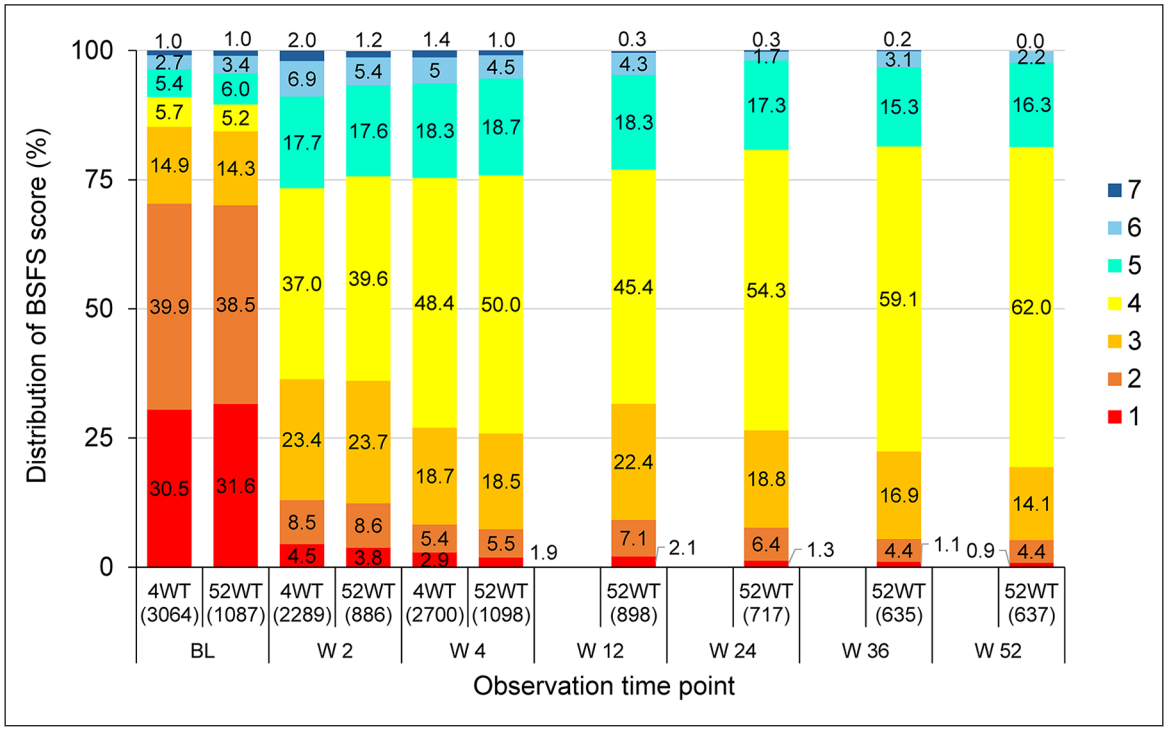

Figure 3. Time course of Bristol Stool Form Scale (BSFS) score distribution in 4-week treatment (4WT) and 52-week treatment (52WT) in the overall population (all age groups). The number in parentheses on the *X*-axis represents the number of patients.
BL: baseline; W: week.

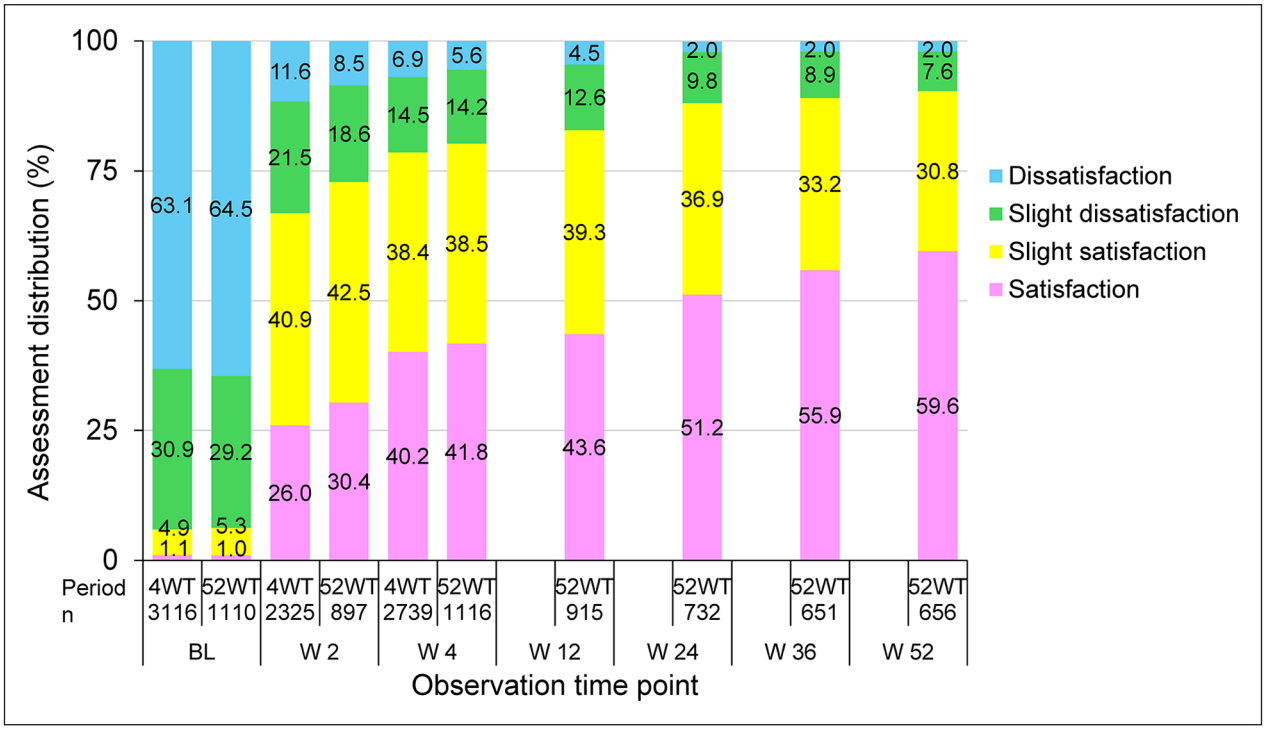

Figure 4. Time course of patient satisfaction assessment in 4-week treatment (4WT) and 52-week treatment (52WT) in the overall population (all age groups). The numbers below the treatment period on the *X*-axis represent the number of patients.
BL: baseline; W: week.

Table 4. Bloating, straining during defecation, fecal disimpaction, and time to defecation in the 4- and 52-week treatment periods.

Constipation-related symptoms	Baseline		Week 2		Week 4		Week 12		Week 24		Week 36		Week 52	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
4-week treatment (*N* = 3410)														
Bloating, N	3016		2284		2679		N/A		N/A		N/A		N/A	
Never	219	(7.3)	513	(22.5)	797	(29.7)								
Rarely	547	(18.1)	937	(41.0)	1155	(43.1)								
Occasionally	1099	(36.4)	617	(27.0)	582	(21.7)								
Frequently	846	(28.1)	167	(7.3)	109	(4.1)								
Always	305	(10.1)	50	(2.2)	36	(1.3)								
Straining during defecation, *N*	2953		2247		2639		N/A		N/A		N/A		N/A	
Never	147	(5.0)	429	(19.1)	637	(24.1)								
Rarely	325	(11.0)	882	(39.3)	1110	(42.1)								
Occasionally	947	(32.1)	623	(27.7)	639	(24.2)								
Frequently	1039	(35.2)	215	(9.6)	165	(6.3)								
Always	495	(16.8)	98	(4.4)	88	(3.3)								
Fecal disimpaction, *N*	3114		2320		2739		N/A		N/A		N/A		N/A	
No	2835	(91.0)	2260	(97.4)*	2674	(97.6)*								
Yes	279	(9.0)	60	(2.6)	65	(2.4)								
Time to defecation[a], *N*	N/A		1359		1551		N/A		N/A		N/A		N/A	
Mean ± SD (h), *n*			6.7 ± 6.5, 1121		6.9 ± 6.4, 1337									
⩽24 h			1106	(81.4)	1325	(85.4)								
⩽48 h			1118	(82.3)	1333	(85.9								
52-week treatment (*N* = 1215)														
Bloating, *N*	1079		889		1102		895		722		635		639	
Never	81	(7.5)	200	(22.5)	326	(29.6)	259	(28.9)	237	(32.8)	213	(33.5)	225	(35.2)
Rarely	197	(18.3)	372	(41.8)	486	(44.1)	400	(44.7)	343	(47.5)	300	(47.2)	307	(48.0)
Occasionally	392	(36.3)	240	(27.0)	239	(21.7)	204	(22.8)	123	(17.0)	107	(16.9)	92	(14.4)
Frequently	290	(26.9)	65	(7.3)	39	(3.5)	24	(2.7)	16	(2.2)	13	(2.0)	14	(2.2)
Always	119	(11.0)	12	(1.3)	12	(1.1)	8	(0.9)	3	(0.4)	2	(0.3)	1	(0.2)
Straining during defecation, *N*	1049		870		1080		884		716		630		632	
Never	51	(4.9)	160	(18.4)	249	(23.1)	225	(25.5)	207	(28.9)	174	(27.6)	191	(30.2)
Rarely	122	(11.6)	351	(40.3)	451	(41.8)	402	(45.5)	341	(47.6)	314	(49.8)	313	(49.5)
Occasionally	343	(32.7)	247	(28.4)	274	(25.4)	196	(22.2)	131	(18.3)	109	(17.3)	93	(14.7)
Frequently	335	(31.9)	68	(7.8)	73	(6.8)	52	(5.9)	30	(4.2)	24	(3.8)	31	(4.9)
Always	198	(18.9)	44	(5.1)	33	(3.1)	9	(1.0)	7	(1.0)	9	(1.4)	4	(0.6)
Fecal disimpaction, *N*	1104		897		1117		932		742		652		653	
No	983	(89.0)	868	(96.8)*	1087	(97.3)*	911	(97.7)*	732	(98.7)*	644	(98.8)*	644	(98.6)*
Yes	121	(11.0)	29	(3.2)	30	(2.7)	21	(2.3)	10	(1.3)	8	(1.2)	9	(1.4)
Time to defecation[a], *N*	N/A		551		651		500		418		382		384	
Mean ± SD (h), *n*			6.0 ± 5.7, 468		6.2 ± 5.6, 566		6.3 ± 7.3, 453		5.8 ± 4.8, 379		5.8 ± 5.2, 355		5.7 ± 5.1, 357	
⩽24 h			465	(84.4)	564	(86.6)	449	(89.8)	377	(90.2)	354	(92.7)	356	(92.7)
⩽48 h			467	(84.8)	565	(86.8)	449	(89.8)	379	(90.7)	354	(92.7)	356	(92.7)

N: number of patients with evaluable data; N/A: not applicable.
[a]Time to defecation after elobixibat administration.
*$p < 0.0001$ versus baseline.

Discussion

Currently, elderly patients aged ⩾65 years account for half of all Japanese patients receiving treatment for CC, with a small sex difference (male:female = 40:60).[17] This study included patients aged ⩾65 years (73.7%), with a similar male-to-female ratio. Therefore, this study may accurately reflect the clinical status of patients with CC.

Regarding safety, the incidence of ADRs was 6.35% in the 4-week treatment period and 5.40% in the 52-week treatment period, both of which were lower than the rates reported in the phase 3 study (30% for 2 weeks and 48% for 52 weeks).[10] The most common ADR was diarrhea (3.35%), followed by abdominal pain (2.06%), which were also the most frequent ADRs observed in phase 2 and 3 studies.[10,13] A meta-analysis reported that the incidence of abdominal pain with elobixibat was high compared with other medications with different mechanisms[18]; this meta-analysis only used data from phase 2 and 3 studies for elobixibat. Based on the results of the present study, abdominal pain may not be a significant consideration in drug selection. Regarding serious ADRs, only one death was recorded. In this case, as it

Table 5. Intraclass correlation coefficients (ICCs) of time to most recent defecation since elobixibat administration in the 52-week treatment period.

ICC [1, *k*]	Time points	*n*	ICC (mean)
ICC [1, 2]	W2 vs W4	420	0.9102
ICC [1, 3]	W2 vs W4 vs W12	274	0.8585
ICC [1, 4]	W2 vs W4 vs W12 vs W24	226	0.8717
ICC [1, 5]	W2 vs W4 vs W12 vs W24 vs W36	203	0.8810
ICC [1, 6]	W2 vs W4 vs W12 vs W24 vs W36 vs W52	189	0.8838

W: week.
ICC [1, *k*] was calculated based on Model 1 for k different observation time points.

Table 6. Assessment of defecation parameters and patient satisfaction according to elobixibat administration timing.

Defecation parameters	Statistics	Administration timing	4-week treatment				52-week treatment			
			Baseline		Week 4		Baseline		Week 52	
Defecation frequency per week	Mean ± SD (*n*)	Before breakfast	2.9 ± 2.2 (1550)		5.5 ± 2.5* (1714)		2.9 ± 2.7 (407)		5.6 ± 2.3* (414)	
		Before lunch	2.9 ± 2.2 (108)		5.1 ± 2.8* (117)		2.8 ± 1.6 (27)		5.8 ± 1.6* (27)	
		Before dinner	2.9 ± 2.2 (507)		5.4 ± 2.6* (572)		2.7 ± 1.5 (106)		5.4 ± 1.9* (113)	
BSFS score	Mean ± SD (*n*)	Before breakfast	2.2 ± 1.4 (1788)		3.9 ± 1.1* (1893)		2.3 ± 1.4 (457)		4.0 ± 0.8* (474)	
		Before lunch	2.4 ± 1.1 (127)		4.0 ± 0.8* (135)		2.2 ± 1.0 (29)		4.1 ± 0.6* (28)	
		Before dinner	2.3 ± 1.3 (611)		3.9 ± 1.0* (653)		2.0 ± 1.0 (123)		3.9 ± 0.9* (126)	
Time to defecation[a] (h)	Mean ± SD (*n*)	Before breakfast	—		5.5 ± 5.5 (931)				4.6 ± 3.3 (268)	
		Before lunch	—		10.3 ± 6.5 (66)				5.7 ± 1.8 (14)	
		Before dinner	—		10.0 ± 7.3 (339)				9.6 ± 8.0 (75)	
Patient satisfaction	*N*	Before breakfast	1820		1921		465		488	
Satisfaction	*n* (%)		12	(0.7)	772	(40.2)	7	(1.5)	295	(60.5)
Slight satisfaction	*n* (%)		74	(4.1)	724	(37.7)	28	(6.0)	144	(29.5)
Slight dissatisfaction	*n* (%)		540	(29.7)	277	(14.4)	129	(27.7)	40	(8.2)
Dissatisfaction	*n* (%)		1194	(65.6)	148	(7.7)	301	(64.7)	9	(1.8)
Patient satisfaction	*N*	Before lunch	127		134		28		27	
Satisfaction	*n* (%)		1	(0.8)	61	(45.5)	0	(0.0)	20	(74.1)
Slight satisfaction	*n* (%)		6	(4.7)	53	(39.6)	2	(7.1)	5	(18.5)
Slight dissatisfaction	*n* (%)		45	(35.4)	15	(11.2)	8	(28.6)	2	(7.4)
Dissatisfaction	*n* (%)		75	(59.1)	5	(3.7)	18	(64.3)	0	(0.0)
Patient satisfaction	*N*	Before dinner	612		662		124		130	
Satisfaction	*n* (%)		10	(1.6)	260	(39.3)	1	(0.8)	69	(53.1)
Slight satisfaction	*n* (%)		51	(8.3)	270	(40.8)	6	(4.8)	50	(38.5)
Slight dissatisfaction	*n* (%)		188	(30.7)	97	(14.7)	37	(29.8)	7	(5.4)
Dissatisfaction	*n* (%)		363	(59.3)	35	(5.3)	80	(64.5)	4	(3.1)

BSFS: Bristol Stool Form Scale; *N*: number of patients with evaluable data.
[a]Time to defecation after elobixibat administration.
*$p < 0.0001$ versus baseline.

was unclear whether the patient took elobixibat, it was difficult to identify the cause of death. All other ADRs were not serious. No specific ADRs were observed in elderly patients. Furthermore, no concerning ADRs, such as decreased body weight or decreased LDL cholesterol were reported even in older age groups with low BMI. This suggests that elobixibat poses minimal risk to patients with frailty or sarcopenia, which would increase in a super-aged society. Thus, the safety of long-term elobixibat use in elderly patients has been confirmed for the first time. Since diarrhea and

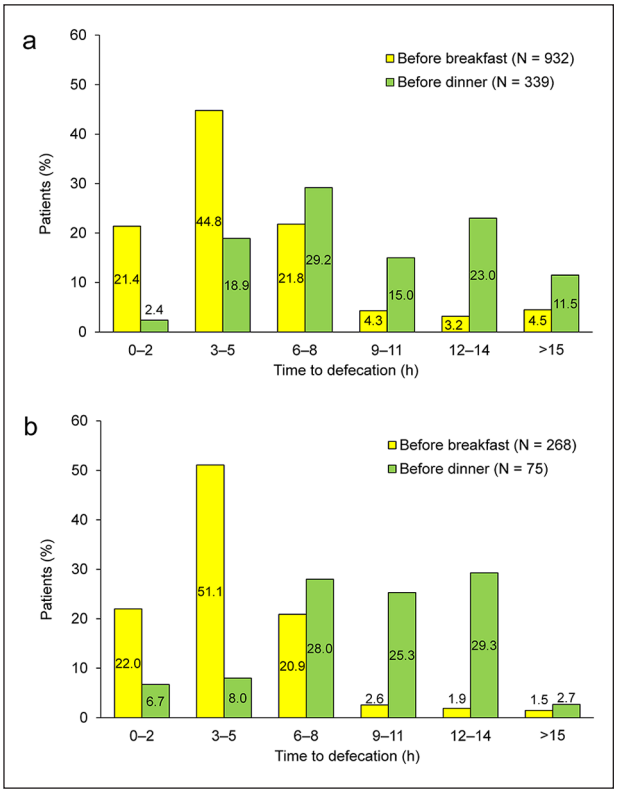

Figure 5. Time to defecation after elobixibat administration before breakfast and dinner in 4-week treatment (a) and 52-week treatment (b).
N: number of patients who reported the time.

Table 7. Proportion of patients who switched to elobixibat monotherapy at the start of elobixibat administration according to the number of laxatives previously prescribed for constipation.

Number of patients	4-week treatment		52-week treatment	
	n	(%)	*n*	(%)
Number of patients with prior laxatives	2125	(100)	772	(100)
Number of patients switching to monotherapy	1026	(48.3)	350	(45.3)
Prior laxatives				
1 drug	793	(37.3)	269	(34.8)
2 drugs	184	(8.7)	64	(8.3)
⩾2 drugs	233	(11.0)	81	(10.5)

abdominal pain are known ADRs, and no serious ADRs occurred, we consider that no specific safety measures are necessary at this time.

The primary efficacy outcomes showed rapid improvement shortly after treatment initiation. The mean defecation frequency doubled to 5 times/week compared with that at baseline. The BSFS score for ideal stool form (Type 4) increased from approximately 6% at baseline to 37% at week 2 and 62% at week 52. The mean BSFS score at each observation point remained around 4 throughout the 52 weeks of treatment. Type 4 stools are most relevant for patient satisfaction in the Patient Assessment of Constipation Quality of Life.[19] Furthermore, it is suggested that Types 3–5 are associated with improved sleep quality.[20] Other outcomes, such as bloating due to constipation, straining during defecation, and fecal disimpaction, also showed improvement from the second week onward. Along with these improvements, the proportion of patients satisfied with defecation increased significantly in this study, which aligns with findings from the long-term phase 3 study in Japan.[10] We believe that, based on their experience, the patient made fine adjustments to the dose and administration timing of elobixibat, which led to bowel movements with appropriate consistency, reduced ADRs, and increased patient satisfaction over time. In addition, treatment discontinuation in patients with a lack of efficacy may also have contributed to the increased proportion of patients showing improvement in these outcomes.

Regarding elobixibat administration timing, the phase 3 study only examined "before breakfast."[10] In contrast, half of the patients in this survey took the drug before breakfast, and the remaining patients took it before lunch or dinner. Notably, no apparent differences in efficacy were observed among the three administration times. The mean time to defecation after elobixibat administration was approximately 6 h throughout the observation period. The proportion of patients defecating within 24 h post-administration was as high (>80%) as in the phase 3 study.[10] This suggests that elobixibat therapy alleviates constipation symptoms quickly and reliably. Patients receiving elobixibat before dinner took a longer time to defecate (delayed defecation) compared with those taking it before breakfast. Considering that defecation during sleep affects quality of life, delayed defecation could be beneficial. However, the time to defecation for each patient remained nearly constant throughout the 52-week observation period, corroborating a small retrospective study.[21] Moreover, most patients chose suitable administration times based on their lifestyle to avoid disrupting sleep or daily activities, took elobixibat at a fixed time, and could predict the time of bowel movement, leading to improved quality of life and patient satisfaction. These patients would no longer worry about defecation timing and could plan daily activities.[22] In addition, predictable bowel movements may increase work productivity[23] and help reduce the burden on caregivers managing the defecation of patients with CC. Therefore, the option of administration timing is considered a patient benefit.

Half of the patients previously using laxatives switched from other laxatives to elobixibat monotherapy at the start of elobixibat administration. This included those who had been taking ⩾2 laxatives prior to initiating elobixibat therapy (11%). With polypharmacy becoming increasingly problematic, particularly in elderly populations, elobixibat's potential to reduce medication burden could contribute to improved polypharmacy management. Throughout the observation period, many patients who started combination therapy with

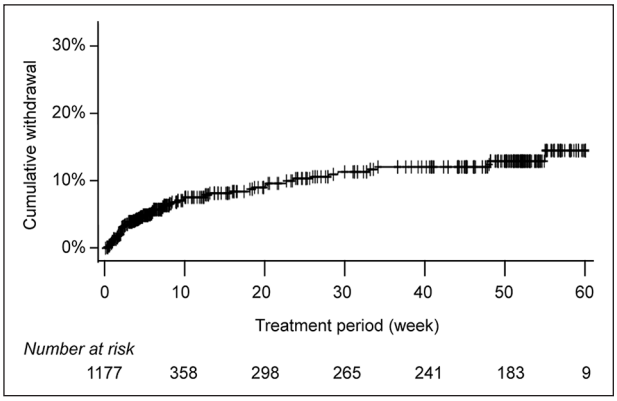

Figure 6. Cumulative proportion of combination drug withdrawal estimated using the Kaplan–Meier method.

elobixibat and other laxatives on day 1 continued this regimen. However, some patients gradually discontinued concomitant other laxatives until 30 weeks in a small proportion, which was 11% at 30 weeks and reached a plateau thereafter. These findings suggest that a period of 30 weeks from a patient initiating combination therapy is the time when the patient can withdraw concomitant other laxatives. After 30 weeks, the patient may need to continue the combination therapy.

This study had some limitations. First, most information regarding initial medical history, safety, and elobixibat's efficacy on defecation was collected through patient interviews, resulting in a substantial number of patients not evaluating various efficacy outcomes. Second, this was a single-arm study without a placebo control. Third, safety and efficacy analyses were conducted irrespective of concomitant laxative use or switching to monotherapy. Fourth, the efficacy of elobixibat may have been overestimated, as some participants discontinued or terminated its use due to the lack of efficacy or occurrence of ADRs. Fifth, efficacy was assessed and summarized based on patient responses to physician interviews using questionnaires. Therefore, patient responses may not necessarily align with defecation status based on objective measurements, except for self-reported patient satisfaction. Lastly, efficacy was assessed without considering disease severity, which was not documented in this study.

Conclusion

This postmarketing study confirmed the long-term safety and favorable efficacy of elobixibat in patients with CC, including elderly ones, in routine clinical practice. Furthermore, three different administration times had minimal impact on efficacy. Based on these findings, we consider the current "Precautions for use" and "Dosage and administration" measures in the product label to be appropriate and sufficient.

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Author contributions statement

Conceptualization and Investigation; Atsushi Nakajima and Yuki Arai; Formal analysis: Masaaki Higashikawa and Yusuke Shimada; Funding acquisition: Yuki Arai; Supervision: Yuki Arai; Writing – original draft preparation: Minami Umeyama; and Writing – review and editing: Atsushi Nakajima, Minami Umeyama, Masaaki Higashikawa, Yusuke Shimada, and Yuki Arai. All authors read and approved the final manuscript.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Minami Umeyama, Masaaki Higashikawa, Yusuke Shimada, and Yuki Arai are current employees of EA Pharma Co., Ltd. Atsushi Nakajima has served as a medical adviser to EA Pharma Co., Ltd.

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Ethics approval

Ethical approval for this study was waived by any ethics committee or institutional review board because this study was conducted in accordance with the Ministry Ordinance on Good Post-Marketing Study Practice issued by the Japanese Ministry of Health, Labor and Welfare, which waives the need for ethical approval. The study protocol was reviewed and approved by the Pharmaceuticals and Medical Devices Agency prior to study initiation.

Consent to participate

Verbal informed consent was obtained from all participants prior to study enrollment.

Informed consent

Verbal informed consent was obtained from all subjects before the study. This survey was conducted in accordance with the Declaration of Helsinki and the Ministry Ordinance on Good Post-Marketing Study Practice issued by the Japanese Ministry of Health, Labor and Welfare, which waived the need for ethical approval, including both written and informed consent, as well as Institutional Review Board approval. However, informed consent was obtained verbally from all participants before study enrollment.

Trial registration

The Japan Registry of Clinical Trials: jRCT1080223950.

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Supplemental material

Supplemental material for this article is available online.

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