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Efficacy and Safety of Elobixibat for Chronic Constipation Based on Rectal Ultrasonography: A Retrospective Observational Study

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Abstract

Background/Objectives: Ultrasonography (US) is a non-invasive and repeatable examination for evaluating chronic constipation. However, only few studies have investigated drug therapy decisions based on rectal US results. To date, the efficacy and safety of elobixibat have not been evaluated using rectal US classification in patients with chronic constipation. This study aimed to evaluate the efficacy and safety of elobixibat in patients with chronic constipation classified as "no fecal retention" by rectal US. **Methods:** We retrospectively analyzed 32 patients with chronic constipation who underwent rectal US and received elobixibat (10 mg/day) between May 2019 and December 2024. Patients were classified into four groups according to rectal US findings: no fecal retention, fecal retention without hard stools, fecal retention with hard stools, and gas retention. The primary endpoint was the response rate of spontaneous bowel movements (SBMs) within 3 days after starting elobixibat in the "no fecal retention" group. **Results:** Among 18 patients in the "no fecal retention" group, 94.4% achieved SBMs within 3 days after elobixibat administration, indicating a favorable response. Adverse events included abdominal distension and abdominal pain, each observed in one patient (3.1%). **Conclusions:** Elobixibat was effective and well tolerated in patients with chronic constipation classified by rectal US findings.

Keywords: constipation; rectal ultrasonography; elobixibat; ileal bile acid transporter; fecal retention; gas retention; retrospective observational study

1. Introduction

In Japan, 2.8% of men and 4.4% of women are reported to experience constipation, which significantly impacts quality of life (QOL) [1–3]. However, constipation is often managed based on patients' subjective complaints, without objective assessment. This leads to poor communication, resulting in mismatched treatment and low patient satisfaction. This dissatisfaction often drives

 doi:10.20944/preprints202510.1402.v1

patients to attempt self-management, leading to treatment that increasingly deviates from appropriate care.

Ultrasonography (US) is a non-invasive examination that can be performed repeatedly. Consequently, US has been considered for evaluating chronic constipation, which often requires repeated assessment [4–6]. Furthermore, the Study Group for US for Chronic Constipation proposed diagnosis and treatment algorithms based on rectal US findings and compiled them into a consensus document [5,7]. The consensus document classifies chronic constipation into three categories ("no fecal retention," "fecal retention without hard stools," and "fecal retention with hard stools") based on rectal US findings and proposes appropriate management for each category.

Elobixibat, an ileal bile acid transporter (IBAT) inhibitor, blocks bile acid reabsorption in the ileum, thereby increasing the amount of bile acids entering the colon [8]. These bile acids increase water and electrolyte influx into the colon, triggering strong bowel movements. In addition, elobixibat lowers rectal sensory thresholds and restores the urge to defecate in patients with chronic constipation [9,10]. Therefore, elobixibat is a promising treatment option for constipation because its mechanism differs from that of conventional laxatives [7,10].

The diagnosis and treatment algorithm for chronic constipation using rectal US findings recommends elobixibat, an IBAT inhibitor, as a first-line treatment for patients with "no fecal retention" whose condition does not improve with lifestyle modification or dietary therapy [7]. This algorithm was developed based on expert opinion as well as drug characteristics. However, few studies have validated this three-category US classification and the corresponding management strategies, indicating the need for further evaluation. Moreover, in real-world practice, the presence of rectal gas cannot be ignored. Rectal evacuation disorder (RED) is a leading cause of intractable constipation not represented in the current three-category classification. Gas retention in the rectum and colon has been reported in patients with RED [11]. In addition, gas retention in the descending colon has also been described among patients reporting incomplete evacuation [12]. These patients may present with features not explained by the three-category classification, indicating that gas-dominant constipation is not well represented in the current system.

This retrospective observational study aimed to evaluate the efficacy and safety of elobixibat in patients with chronic constipation classified as "no fecal retention" by rectal US. Furthermore, the study addressed gas-dominant constipation by expanding the conventional three-category classification to four categories through the addition of "gas retention": "no fecal retention," "fecal retention without hard stools," "fecal retention with hard stools," and "gas retention." We retrospectively analyzed patients with chronic constipation who underwent rectal US and received elobixibat and evaluated treatment outcomes according to this four-category classification. This study demonstrates that rectal US-based classification, especially the "no fecal retention" category, provides a practical framework for guiding elobixibat therapy in patients with chronic constipation.

2. Materials and Methods

2.1. Study Participants

This retrospective observational study utilized data collected between May 2019 and December 2024 at Hakodate Medical Center and Sapporo Cancer Screening Center. The study enrolled 32 patients aged ≥18 years with chronic constipation who underwent rectal US and received elobixibat. Patients who underwent rectal US on the day before the first elobixibat administration and received the drug at the recommended dose of 10 mg/day were included. The exclusion criteria were as follows: a history of hypersensitivity to elobixibat; confirmed or suspected intestinal obstruction due to tumors, hernia, or other causes; suspected constipation secondary to organic disease; or the use of intestinal cleansing agents, enemas, or bowel lavage from 2 days before to 3 days after rectal US.

 doi:10.20944/preprints202510.1402.v1

2.2. Observation Period and Data Collection

Patient data were collected from the day before elobixibat initiation until 2 weeks after treatment. Information was collected from medical records and questionnaires, including age, sex, height, weight, comorbidities, prior medications, rectal US findings, colonic diameters, elobixibat dosing, spontaneous bowel movements (SBMs) during the first 3 days after elobixibat initiation, Bristol Stool Form Scale (BSFS), Constipation Scoring System (CSS), and adverse events [13,14].

2.3. Assessment of Bowel Movements

Bowel function was assessed by documenting the presence or absence of SBMs during the first 3 days after elobixibat initiation using patient questionnaires. SBMs were defined as bowel movements occurring without the use of bisacodyl suppositories, enemas, or digital disimpaction. Patients who experienced SBMs within this period were defined as responders.

2.4. Stool Form and Constipation Scoring

Stool consistency and constipation severity were evaluated using the BSFS and calculated modified CSS scores, respectively, based on entries in medical records and questionnaires. The modified CSS total score was calculated by subtracting the item "duration of constipation" from the CSS total score. Both BSFS and CSS were assessed at baseline and 2 weeks after treatment.

2.5. Ultrasonography (US)

Rectal ultrasound images were obtained using an Aplio i700® system (Canon Medical Systems, Japan) equipped with a convex probe (PVI-475BX). Imaging conditions were set as follows: depth, 14–21 cm; frequency, 4.0 MHz; gain, 73–80 dB; and dynamic range, 60 dB. Rectal US was performed in the supine position using a transabdominal approach with the probe placed on the suprapubic region.

2.6. Rectal US Classification

To classify rectal findings, the conventional three-category classification (no fecal retention, fecal retention without hard stools, and fecal retention with hard stools) was expanded by adding a fourth category, "gas retention." The "gas retention" category was defined as the presence of multiple echoes with reverberation artifacts in the rectum on transabdominal US (Figure 1).

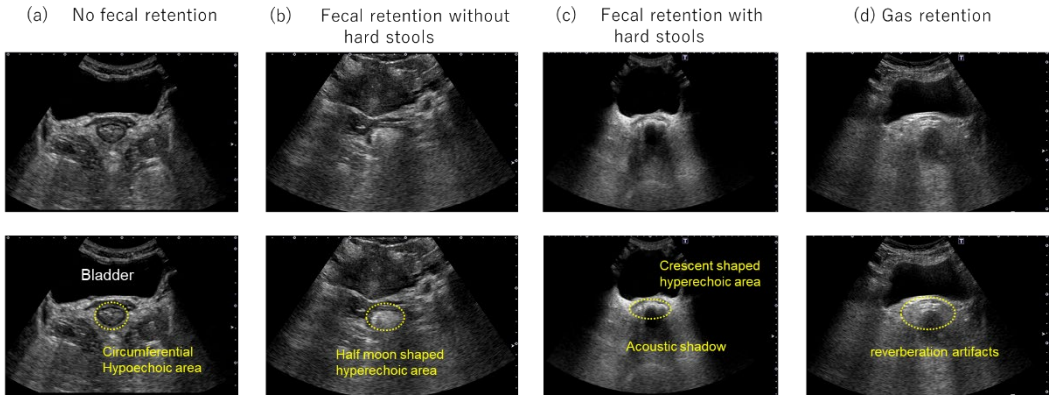

Figure 1. Transverse rectal ultrasound images. (a) No fecal retention, with no hyperechoic area observed. A circumferential hypoechoic area is observed in the lower part of the bladder. (b) Fecal retention without hard stools, revealing a half-moon-shaped hyperechoic area in the lower part of the bladder. (c) Fecal retention with hard stools, revealing a crescent-shaped hyperechoic area with an acoustic shadow in the lower part of the bladder. (d) Gas retention, multiple echoes with reverberation artifacts are observed in the lower part of the bladder.

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2.7. Measurement of Colonic Diameter

To measure colonic diameter, US was performed at five sites: ascending colon, transverse colon, descending colon, sigmoid colon, and rectum [4]. Up to three measurements (proximal, middle, and distal) were obtained for each site. The diameter for each site was calculated as the average of its measurements, and the mean colonic diameter was obtained by averaging across all sites. Colonic diameter was assessed at baseline only.

2.8. Statistical Analysis

All analyses were conducted using R (version 4.4.1; R Core Team, 2024). Continuous variables are summarized as means with standard deviations or medians with interquartile ranges and categorical variables as frequencies and percentages. The Wilson score method was used to calculate 95% confidence intervals (CIs). Before-and-after values were compared using the Wilcoxon signed-rank test. A two-sided p-value < 0.05 was considered statistically significant. A correlation analysis was conducted to examine the association between mean colonic diameter and rectal US classification. For this analysis, only patients with measurements available for all five colonic regions were included. We used linear regression models were used with "no fecal retention" as the reference group to estimate differences in transverse diameter.

3. Results

3.1. Patient Enrollment and Analysis Sets

During the study period, 249 patients underwent rectal US, and 110 were prescribed elobixibat after the procedure. Among them, 32 patients met the eligibility criteria and were enrolled in the study. All 32 patients were included in the safety analysis set. One patient with a colostomy was excluded from the efficacy analysis set, leaving 31 patients for efficacy evaluation. Based on rectal US findings, 18 patients were classified as "no fecal retention," 1 as "fecal retention without hard stools," 2 as "fecal retention with hard stools," and 8 as "gas retention." Rectal US findings could not be visualized in two patients (Figure 2).

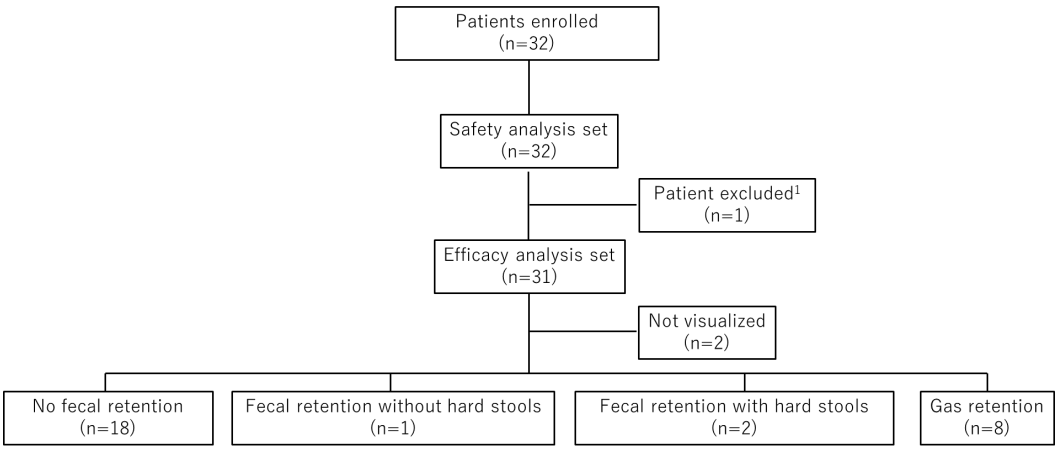

Figure 2. Patient flow diagram. Thirty-two patients were enrolled, of whom 32 were included in the safety analysis set and 31 in the efficacy analysis set. Patients were classified into four rectal US categories: no fecal retention (n = 18), fecal retention without hard stools (n = 1), fecal retention with hard stools (n = 2), and gas retention (n = 8). [1] One patient with a colostomy was excluded because rectal US classification could not be performed.

 doi:10.20944/preprints202510.1402.v1

3.2. Patient Characteristics

Patient characteristics are summarized in Table 1. Most patients were female in both the efficacy and safety analysis sets. The mean age was 56.8 years in the efficacy set and 56.5 years in the safety set. Baseline bowel movement data (median) for the efficacy and safety sets, respectively, were as follows: BSFS score, 1.0 and 1.0; CSS total score, 13.5 and 13.5; and modified CSS total score, 10.0 and 10.0. CSS sub-scores were as follows: frequency of bowel movements, 1.0 and 1.0; painful evacuation effort, 2.0 and 2.0; feeling of incomplete evacuation, 3.0 and 3.0; abdominal pain, 1.0 and 1.0; minutes in lavatory per attempt, 1.0 and 1.0; type of assistance, 1.0 and 1.0; unsuccessful evacuation attempts per 24 hours, 1.0 and 1.0; and duration of constipation, 3.0 and 3.0 (Table 1).

Table 1. Patient characteristics.

Data	Efficacy Analysis Set		Safety Analysis Set	
	N	Variable	N	Variable
Subjects	31		32	
Male, n (%)[1]		6 (19.4)		6 (18.8)
Female, n (%)[1]		25 (80.6)		26 (81.3)
Age (years), mean ± SD	31	56.8 ± 14.7	32	56.5 ± 14.6
Height (cm), mean ± SD	31	157.68 ± 7.19	32	157.56 ± 7.10
Weight (kg), mean ± SD	31	55.51 ± 11.96	32	55.18 ± 11.91
Rectal US classification	31		32	
No fecal retention, n (%)[1]		18 (58.1)		18 (56.3)
Fecal retention without hard stools, n (%)[1]		1 (3.2)		1 (3.1)
Fecal retention with hard stools, n (%)[1]		2 (6.5)		2 (6.3)
Gas retention, n (%)[1]		8 (25.8)		8 (25.0)
Not visualized, n (%)[1, 2]		2 (6.5)		3 (9.4)
BSFS, median (IQR)	30	1.0 (1.0–3.0)	31	1.0 (1.0–4.0)
CSS				
Frequency of bowel movements, median (IQR)	30	1.0 (0.0–2.0)	31	1.0 (0.0–2.0)
Painful evacuation effort, median (IQR)	30	2.0 (0.0–3.0)	31	2.0 (0.0–3.0)
Feeling of incomplete evacuation, median (IQR)	30	3.0 (2.0–4.0)	31	3.0 (2.0–4.0)
Abdominal pain, median (IQR)	30	1.0 (0.0–2.0)	31	1.0 (0.0–2.0)
Minutes in lavatory per attempt, median (IQR)	30	1.0 (1.0–2.0)	30	1.0 (1.0–2.0)
Type of assistance, median (IQR)	30	1.0 (1.0–2.0)	31	1.0 (1.0–2.0)
Unsuccessful evacuation attempts per 24 hours, median (IQR)	30	1.0 (1.0–1.0)	30	1.0 (1.0–1.0)
Duration of constipation, median (IQR)	30	3.0 (2.0–4.0)	31	3.0 (2.0–4.0)
CSS total score, median (IQR)	30	13.5 (10.0–17.0)	30	13.5 (10.0–17.0)
Modified CSS total score, median (IQR)	30	10.0 (8.0–13.0)	30	10.0 (8.0–13.0)
Colonic diameter				
Rectum (mm), mean ± SD	20	34.15 ± 13.18	20	34.15 ± 13.18
Ascending colon (mm), mean ± SD	24	35.70 ± 6.83	25	35.58 ± 6.72
Transverse colon (mm), mean ± SD	20	24.29 ± 3.34	21	24.35 ± 3.26
Descending colon (mm), mean ± SD	22	22.49 ± 4.02	23	22.26 ± 4.08
Sigmoid colon (mm), mean ± SD	22	21.80 ± 3.49	23	21.71 ± 3.43
Mean colonic diameter (mm), mean ± SD	24	28.32 ± 6.36	25	28.14 ± 6.29
Comorbidities[3]	31		32	
Yes, n (%)[1]		13 (41.9)		14 (43.8)
Mental disorder, n (%)[1]		3 (9.7)		3 (9.4)
After cancer surgery, n (%)[1]		2 (6.5)		3 (9.4)
Cholecystectomy, n (%)[1]		1 (3.2)		1 (3.1)
Others, n (%)[1, 4]		8 (25.8)		8 (25.0)
No, n (%)[1]		18 (58.1)		18 (56.3)
Prior medications for constipation[3, 5]	31		32	
Yes, n (%)[1]		22 (71.0)		23 (71.9)
Osmotic laxatives, n (%)[1]		12 (38.7)		12 (37.5)
Stimulant laxatives, n (%)[1]		13 (41.9)		14 (43.8)
Intestinal secretagogues, n (%)[1, 6]		2 (6.5)		2 (6.3)
Others, n (%)[1, 7]		4 (12.9)		4 (12.5)
No, n (%)[1]		9 (29.0)		9 (28.1)
Prior medications for other comorbidities[5]	31		32	
Yes, n (%)[1]		17 (54.8)		18 (56.3)
No, n (%)[1]		14 (45.2)		14 (43.8)

 doi:10.20944/preprints202510.1402.v1

[1]Percentages are calculated based on the number of patients in each analysis set. [2]Includes one patient excluded from the efficacy analysis set. [3]Includes duplicate entries. [4]Includes anemia, endometriosis, gastroesophageal reflux disease*, hypothyroidism, intracranial aneurysm*, Ménière's disease, pneumothorax, uterine leiomyoma, and endolymphatic hydrops, each in one patient. Conditions marked with an asterisk (*) occurred in the same patient. [5]Indicates whether any medication was used within two weeks prior to the first dose of elobixibat [6]Includes lubiprostone and linaclotide, each in one patient. [7]Includes Chinese traditional or herbal medicines in three patients, and enemas and probiotics in one patient each. One patient had received both Chinese traditional or herbal medicines and probiotics. Abbreviations: BSFS, Bristol Stool Form Scale; CSS, Constipation Scoring System; US, ultrasonography.

3.3. Proportion of Responders with SBMs Within 3 Days After the First Dose of Elobixibat

The primary endpoint was the proportion of responders in the "no fecal retention" category who had SBMs within 3 days after the first dose of elobixibat. In this category, 94.4% (95% CI, 74.2%–99.0%) achieved SBMs. Response rates were also 100% in the "fecal retention without hard stools" (95% CI, 20.7%–100.0%), "fecal retention with hard stools" (95% CI, 34.2%–100.0%), and "gas retention" (95% CI, 67.6%–100.0%) categories. Overall, the response rate across all four categories was 96.6% (95% CI, 82.8%–99.4%) (Table 2). Both patients whose rectal US findings were not visualized also responded (data not shown).

Table 2. Proportion of responders with spontaneous bowel movements (SBMs) within 3 days after the first dose of elobixibat.

Rectal US Classification	N	Responder, (n)	Non-Responder, (n)	Proportion of Responders[1, 2] (%)	95% CI[3] (%)
No fecal retention	18	17	1	94.4	74.2–99.0
Fecal retention without hard stools	1	1	0	100.0	20.7–100.0
Fecal retention with hard stools	2	2	0	100.0	34.2–100.0
Gas retention	8	8	0	100.0	67.6–100.0
Total of 4 categories	29	28	1	96.6	82.8– 99.4

[1]Responders were defined as patients who had at least one SBM within 3 days after the first dose of elobixibat without the use of suppositories (e.g., bisacodyl), enemas, or digital disimpaction. [2]Values are expressed as percentages based on the number of patients in each rectal US classification. [3]CIs were calculated using the Wilson score method. Abbreviations: CI, confidence interval; US, ultrasonography.

3.4. Proportion of Responders with SBMs on Day 1 Following the First Dose of Elobixibat

On day 1, 83.3% (95% CI, 60.8%–94.2%) of patients in the "no fecal retention" category achieved SBMs. Response rates were 100% in the "fecal retention with hard stools" (95% CI, 34.2%–100.0%) and "gas retention" (95% CI, 67.6%–100.0%) categories. Overall, the response rate across all four categories was 89.3% (95% CI, 72.8%–96.3%) (Table 3).

Table 3. Proportion of responders with spontaneous bowel movements (SBMs) on day 1 following the first dose of elobixibat.

Rectal US Classification	N	Responder, (n)	Non-Responder, (n)	Proportion of Responders[1, 2] (%)	95% CI[3] (%)
No fecal retention	18	15	3	83.3	60.8–94.2
Fecal retention without hard stools	0	0	0	-	-
Fecal retention with hard stools	2	2	0	100.0	34.2–100.0
Gas retention	8	8	0	100.0	67.6–100.0
Total of 4 categories	28	25	3	89.3	72.8–96.3

[1]Responders were defined as patients who had at least one SBM on day 1 without the use of suppositories (e.g., bisacodyl), enemas, or digital disimpaction. [2]Values are expressed as percentages based on the number of patients in each rectal US classification. [3]CIs were calculated using the Wilson score method. Abbreviations: CI, confidence interval; US, ultrasonography.

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3.5. Stool Consistency Outcomes (BSFS)

Changes in stool consistency were evaluated using the BSFS. In patients classified as "no fecal retention," the median BSFS scores were 1.5 (1.0–5.0) at baseline and 4.0 (2.5–5.0) at week 2, showing no significant difference. In the "fecal retention with hard stools" category, the BSFS scores were 1.5 (1.0–2.0) at baseline and 1.0 (1.0–1.0) at week 2, showing no improvement. In contrast, patients in the "gas retention" category demonstrated a significant improvement in BSFS scores from 1.0 (1.0–3.0) at baseline to 4.0 (2.5–4.5) at week 2 ($p = 0.0350$). When analyzed across all four categories, BSFS scores significantly improved from 1.0 (1.0–3.5) at baseline to 4.0 (2.0–5.0) at week 2 ($p = 0.0104$) (Table 4).

Table 4. Stool consistency outcomes (BSFS).

Rectal US Classification	Baseline		Week 2		
	N	Variable	N	Variable	p^1
No fecal retention, median (IQR)	18	1.5 (1.0–5.0)	16	4.0 (2.5–5.0)	0.1078
Fecal retention without hard stools, median (IQR)	1	1.0 (1.0–1.0)	0	-	-
Fecal retention with hard stools, median (IQR)	2	1.5 (1.0–2.0)	2	1.0 (1.0–1.0)	1.0000
Gas retention, median (IQR)	7	1.0 (1.0–3.0)	8	4.0 (2.5–4.5)	0.0350*
Total of 4 categories, median (IQR)	28	1.0 (1.0–3.5)	26	4.0 (2.0–5.0)	0.0104*

* $p < 0.05$. [1] Wilcoxon signed-rank test. Abbreviations: US, ultrasonography.

We also analyzed the distribution of stool consistency in the total cohort. The proportion of patients with a BSFS score of 1 or 2 decreased from 71.4% (20/28 patients) at baseline to 30.8% (8/26 patients) after elobixibat treatment. The proportion of patients with a BSFS score of 3–5 increased from 21.4% (6/28 patients) to 57.7% (15/26 patients), and that of patients with a BSFS score of 6 or 7 increased from 7.1% (2/28 patients) to 11.5% (3/26 patients). These findings indicate that elobixibat shifted stool consistency toward normal or softer stools (Figure 3).

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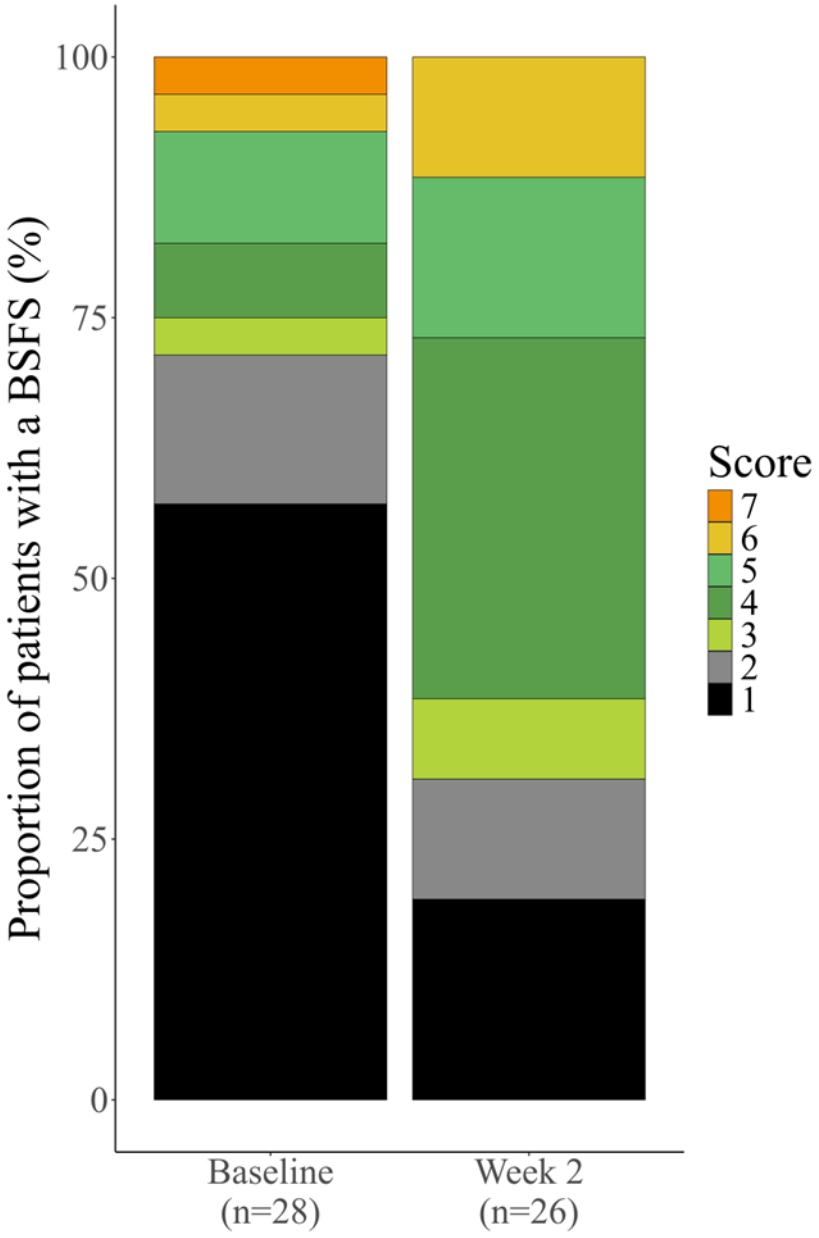

Figure 3. Distribution of stool consistency in all four categories combined. BSFS score definitions:. 1 = separate hard lumps, like nuts; 2 = sausage-shaped but lumpy; 3 = like a sausage or snake but with cracks on its surface; 4 = like a sausage or snake, smooth and soft; 5 = soft blobs with clear-cut edges; 6 = fluffy pieces with ragged edges, a mushy stool; 7 = watery, no solid pieces. Data were compiled excluding patients with "Not evaluated" BSFS scores (baseline, n = 1; week 2, n = 3). Abbreviation: BSFS, Bristol Stool Form Scale.

3.6. Constipation Scoring System (CSS) Outcomes

3.6.1. Modified CSS Total Score

Changes in the modified CSS total score were evaluated. In patients classified as "no fecal retention," the median score decreased from 10.0 (7.0–14.0) at baseline to 8.0 (6.0–12.0) at week 2, with no significant difference. In the "fecal retention without hard stools" and "fecal retention with hard stools" categories, scores showed no consistent trend. In patients classified as "gas retention," the score decreased from 10.0 (6.0–10.0) at baseline to 6.0 (3.0–11.5) at week 2, but the change was not statistically significant ($p = 0.0502$). When analyzed across all four categories, the modified CSS total score significantly decreased from 10.0 (7.5–13.5) at baseline to 8.5 (5.0–12.0) at week 2 ($p = 0.0231$) (Table 5).

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Table 5. Modified Constipation Scoring System (CSS) total score.

Rectal US Classification	Baseline		Week 2		
	N	Variable	N	Variable	p^1
No fecal retention, median (IQR)	18	10.0 (7.0–14.0)	17	8.0 (6.0–12.0)	0.2206
Fecal retention without hard stools, median (IQR)	1	10.0 (10.0–10.0)	1	11.0 (11.0–11.0)	1.0000
Fecal retention with hard stools, median (IQR)	2	16.5 (13.0–20.0)	2	11.5 (11.0–12.0)	0.3711
Gas retention, median (IQR)	7	10.0 (6.0–10.0)	8	6.0 (3.0–11.5)	0.0502
Total of 4 categories, median (IQR)	28	10.0 (7.5–13.5)	28	8.5 (5.0–12.0)	0.0231*

* $p < 0.05$. [1] Wilcoxon signed-rank test. Abbreviations: CSS, Constipation Scoring System; US, ultrasonography.

3.6.2. Modified CSS Sub-Scores

Changes in individual CSS sub-scores were also examined. No significant differences were observed in any sub-score when patients were classified by rectal US classification (data not shown).

However, when analyzed across all four categories, the sub-score "minutes in lavatory per attempt" showed significant improvement after elobixibat treatment ($p = 0.0046$). No other sub-scores demonstrated significant changes (Table 6, Figure 4).

Table 6. Modified Constipation Scoring System (CSS) sub-scores.

Rectal US Classification	CSS Sub-Score	Timepoint	N	Variable, Median (IQR)	p^1
Total of 4 categories	Total score (excluding the duration of constipation)[2]	Baseline	28	10.0 (7.5–13.5)	0.0231*
		Week 2	28	8.5 (5.0–12.0)	
	Frequency of bowel movements	Baseline	28	0.5 (0.0–1.5)	0.3543
		Week 2	28	0.0 (0.0–1.0)	
	Painful evacuation effort	Baseline	28	2.0 (0.0–3.0)	0.6806
		Week 2	28	2.0 (0.0–3.0)	
	Feeling of incomplete evacuation	Baseline	28	3.0 (2.0–4.0)	0.0615
		Week 2	28	2.5 (1.0–3.0)	
	Abdominal pain	Baseline	28	1.0 (0.0–2.0)	0.1078
		Week 2	28	2.0 (0.5–2.0)	
	Minutes in lavatory per attempt	Baseline	28	1.0 (0.5–2.0)	0.0046*
		Week 2	28	0.5 (0.0–1.0)	
	Type of assistance	Baseline	28	1.0 (1.0–2.0)	0.0782
		Week 2	28	1.0 (0.0–1.0)	
	Unsuccessful evacuation attempts per 24 hours	Baseline	28	1.0 (1.0–1.0)	0.0519
		Week 2	28	1.0 (0.5–1.0)	

* $p < 0.05$. [1] Wilcoxon signed-rank test. [2] Modified CSS Abbreviations: CSS, Constipation Scoring System; US, ultrasonography.

 doi:10.20944/preprints202510.1402.v1

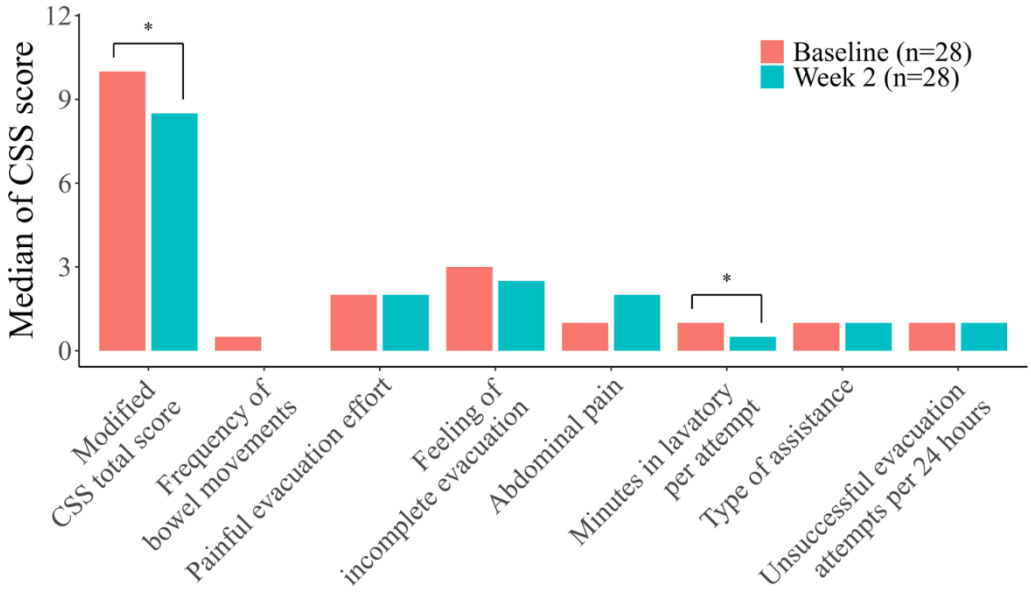

Figure 4. Modified Constipation Scoring System (CSS) sub-scores in all four categories combined. Statistical analyses were performed using the Wilcoxon signed-rank test. Bars indicate items with statistically significant changes. * $p < 0.05$ Abbreviations: CSS, Constipation Scoring System.

3.7. Relationship Between Colonic Diameter and Rectal US Classification

The relationship between the mean transverse colonic diameter and rectal US classification was evaluated. The mean diameter was 25.00 ± 1.23 mm in patients with "no fecal retention," 33.09 ± 5.88 mm in those with "fecal retention with hard stools," and 28.86 ± 1.43 mm in those with "gas retention." The overall mean diameter across all four categories was 27.31 ± 3.41 mm. In the "fecal retention without hard stools" category, no measurements were available (Table 7). A correlation ratio of 0.694 was observed between the total classification and mean transverse diameter, indicating a positive association (Table S1).

Table 7. Mean transverse colonic diameter stratified by rectal ultrasonography (US) classification.

Rectal US Classification	Number of Patients	Mean Transverse Diameter of the Colon and Rectum[1] (mm)
	N[2]	Variable
No fecal retention, Mean ± SD	9	25.00 ± 1.23
Fecal retention without hard stools, Mean ± SD	-	-
Fecal retention with hard stools, Mean ± SD	2	33.09 ± 5.88
Gas retention, Mean ± SD	6	28.86 ± 1.43
Total of 4 categories, Mean ± SD	17	27.31 ± 3.41

[1] The mean transverse colonic diameter is presented as mean ± SD. [2] Number of patients in whom all five regions (ascending colon, transverse colon, descending colon, sigmoid colon and rectum) were successfully measured. Abbreviations: US, ultrasonography.

Linear regression analysis showed that the mean transverse diameter was significantly greater in patients with "fecal retention with hard stools" ($p = 0.0002$) or "gas retention" ($p = 0.0027$) than in those without fecal retention (Table 8).

Table 8. Prediction of transverse colonic diameter by rectal US classification (linear regression analysis).

Factor	Estimated Difference[1]	95% CI	*p*
Rectal US classification: fecal retention without hard stools	-	-	-

 doi:10.20944/preprints202510.1402.v1

Rectal US classification: fecal retention with hard stools	8.09	[4.705–11.468]	0.0002*
Rectal US classification: gas retention	3.86	[1.579–6.139]	0.0027*

* $p < 0.05$. [1] Estimated difference determined by subtracting the "no fecal retention" group from each respective category. Abbreviations: CI, confidence interval; US, ultrasonography.

3.8. Safety

Adverse events occurred in two patients (6.3%) in the safety analysis set (Table 9). All events were mild and resolved without intervention. No serious adverse events occurred, and no patients discontinued elobixibat during the 2-week observation period.

Table 9. Adverse events in the safety analysis set.

			Total	Severity		
				Mild	Moderate	Severe
			n (%)	n (%)	n (%)	n (%)
Number			32	32	32	32
Adverse event			2 (6.3)	2 (6.3)	0 (0.0)	0 (0.0)
	Gastrointestinal disorders		2 (6.3)	2 (6.3)	0 (0.0)	0 (0.0)
		Abdominal distension	1 (3.1)	1 (3.1)	0 (0.0)	0 (0.0)
		Abdominal pain	1 (3.1)	1 (3.1)	0 (0.0)	0 (0.0)

Adverse events are expressed as percentages of the total number of patients in the safety analysis set. Medical Dictionary for Regulatory Activities/J (MedDRA/J) version 27.1. Abbreviations: MedDRA/J, Medical Dictionary for Regulatory Activities/J.

4. Discussion

This study demonstrated that elobixibat was highly effective and well tolerated in patients with chronic constipation, particularly in those categorized as "no fecal retention" on rectal US. The primary endpoint, defined as the proportion of responders achieving SBMs within 3 days of the first dose, was 94.4% in this group, underscoring the rapid therapeutic benefit of elobixibat. Early symptom relief is clinically relevant because it improves treatment adherence and patient satisfaction. The day 1 response rate (83.3%) was also consistent with previous Phase 3 data, supporting the reproducibility of our findings [15].

The therapeutic benefit in the "no fecal retention" group can be explained by the unique pharmacological properties of elobixibat. Unlike conventional laxatives, elobixibat promotes bowel movements through multiple mechanisms: inhibition of IBAT to increase bile acid flow and fluid secretion, acceleration of large intestinal motility, and restoration of the urge to defecate [9,10]. Kessoku et al. recently reported that, in patients with "no fecal retention," elobixibat significantly improved complete SBMs, colonic transit time, and the urge to defecate compared with magnesium oxide [16]. Other studies have also shown that elobixibat enables switching from, or reducing the dose of, stimulant laxatives [17,18]. Together, these findings highlight elobixibat's clinical value as a first-line therapy for patients without fecal retention.

Patients with rectal gas retention also responded favorably to elobixibat, suggesting its potential role in gas-dominant constipation. In this category, all patients achieved SBMs within 3 days, and stool form improved significantly to BSFS type 4 by week 2. Since gas retention has been associated with rectal evacuation disorder and incomplete evacuation, these results suggest that elobixibat may be effective in a subset of patients not fully represented in the current three-category algorithm [11,12]. For such conditions, decreased rectal sensation has been proposed as an underlying mechanism [19]. Elobixibat has been reported to improve rectal sensory thresholds and may thus be particularly effective for constipation accompanied by gas retention [9]. However, structural defecatory disorders, such as rectocele or megacolon, cannot be excluded by rectal US alone, and complementary diagnostic modalities remain necessary [6].

 doi:10.20944/preprints202510.1402.v1

The impact of rectal US classification was further reflected in colonic diameter measurements. Patients in the "fecal retention with hard stools" and "gas retention" categories had significantly larger transverse colonic diameters than those in the "no fecal retention" group, indicating that both hard stool and gas retention are physiologically linked with upstream colonic dilatation. This supports the clinical utility of rectal US as a noninvasive tool for stratifying constipation phenotypes.

Elobixibat was generally safe and well tolerated in this cohort. Only two patients (6.3%) reported mild gastrointestinal adverse events (abdominal distension and abdominal pain), both resolving spontaneously without discontinuation. This profile aligns with previous clinical trials, underscoring the suitability of elobixibat for the long-term management of chronic constipation [15,20].

Several limitations of this study should be noted. The retrospective design and small sample size limit the strength of causal inference. The observation period was short, focusing only on early outcomes; thus, long-term improvements in stool consistency, symptom severity and QOL could not be assessed. Prior studies have demonstrated the sustained efficacy of elobixibat over longer follow-up periods [21,22]. Moreover, as this study was conducted exclusively in Japan, the generalizability of the findings to other populations remains uncertain. Future studies will need to validate these findings in larger, prospective, multicenter cohorts and should explore long-term outcomes, including stool consistency, symptom severity, and QOL. In addition, further research will clarify the role of gas-dominant constipation and refine rectal US–based treatment algorithms for broader clinical application.

Elobixibat showed clear and rapid efficacy in patients with chronic constipation, particularly in those with "no fecal retention" on rectal US. Patients with rectal gas retention also benefited, highlighting the value of incorporating this category into diagnostic algorithms. These findings support rectal US-based classification as a practical tool for guiding treatment and confirm elobixibat as an effective first-line option for patients without fecal retention

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Correlation analysis between mean transverse colonic diameter Ultrasonography (US) diagnostic classification.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. In addition, prior to study initiation, the protocol was approved by the Ethics Committees of the National Hospital Organization, Hakodate Medical Center (approval code, R6-1206001; date of approval, December 6, 2024) and the Hokkaido Cancer Society, Sapporo Cancer Screening Center (approval code, 2024-008; date of approval, December 27, 2024). The study was registered with UMIN-CTR on January 6, 2025 [UMIN000056635].

Informed Consent Statement: No informed consent was required since this was a retrospective study performed using existing information [Ethical Guidelines for Medical and Biological Research Involving Human Subjects]. Information on the study was posted on the websites of the participating medical institutions for a period of 3 months to ensure that potentially eligible patients had the opportunity to opt out of participation in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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Conflicts of Interest: M.T. has received honoraria from EA Pharma Co., Ltd. S. K. and Y. H. are employees of EA Pharma Co., Ltd. The other authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BSFS	Bristol stool form scale
CSS	Constipation scoring system
CI	Confidence Interval
IBAT	Ileal bile acid transporter
MedDRA/J	Medical Dictionary for Regulatory Activities/J
QOL	Quality of life
RED	Rectal evacuation disorder
SBM	Spontaneous bowel movement
US	Ultrasonography

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