A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis

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ABSTRACT

Background. JTT-751 is a novel phosphate binder containing ferric citrate as the active ingredient.

Methods. In this Phase 3, multicenter, randomized, open-label, parallel-group study, we compared the efficacy and safety of JTT-751 and sevelamer hydrochloride in patients undergoing hemodialysis. A total of 230 patients with a serum phosphate ≥1.97 and <3.23 mmol/L were randomized to JTT-751 (dose adjusted between 1.5 and 6.0 g/day) or sevelamer hydrochloride (dose adjusted between 3.0 and 9.0 g/day) for 12 weeks. The primary outcome was change in serum phosphate from baseline to end of treatment. Secondary outcomes included the changes in corrected serum calcium and intact parathyroid hormone (PTH). The changes in ferritin,
transferrin saturation and erythropoiesis-stimulating agent dose were additional outcomes.

Results. Changes in serum phosphate at the end of treatment were \(-0.82\) mmol/L in the JTT-751 group and \(-0.78\) mmol/L in the sevelamer group, establishing non-inferiority of JTT-751 compared with sevelamer (least squares mean, \(-0.03\) mmol/L; 95% confidence interval, \(-0.13\) to 0.07 mmol/L). Corrected serum calcium increased and PTH decreased from baseline within both groups; changes between groups were similar. Gastrointestinal disorders were the most common adverse events in both groups; the incidence of diarrhea was higher in the JTT-751 group, while constipation occurred frequently in the sevelamer group. Treatment with JTT-751 resulted in significant relative increases in serum ferritin and transferrin saturation.

Conclusions. Efficacy and safety of JTT-751 was comparable to sevelamer in patients on hemodialysis with hyperphosphatemia. Differential adverse effects were observed; biochemical markers of iron status increased in patients treated with JTT-751.

Trial registration number. CTI-111433 (The Japan Pharmaceutical Information Center at: http://www.clinicaltrials.jp). Date of registration: 7 March 2011.

Keywords: clinical trial, ferric citrate, hemodialysis, hyperphosphatemia, phosphate binder

INTRODUCTION

In patients with end-stage renal disease (ESRD), hyperphosphatemia contributes to secondary hyperparathyroidism and can lead to skeletal complications including fracture, and extraskeletal (ectopic) calcification of soft tissues, including the arterial tree, with serious clinical consequences. Vascular calcification and resultant vascular stiffness have been linked to changes in ventricular structure and function and cardiovascular events, including heart failure and sudden death [1–4]. Control of hyperphosphatemia is recommended by clinical practice guidelines worldwide. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended maintaining serum phosphate concentrations within 3.5–5.5 mg/dL (1.13–1.78 mmol/L) [5]; the Japanese Society for Dialysis Therapy (JSDT) CKD-Mineral and Bone Disorders guidelines advise that serum phosphate concentrations 3 days after the last hemodialysis session be kept within the range of 3.5–6.0 mg/dL (1.13–1.94 mmol/L) [6]; the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest lowering serum phosphate concentrations toward the normal range [7].

Currently employed phosphate binders include calcium carbonate, acetate and citrate, sevelamer carbonate and hydrochloride and lanthanum carbonate; aluminum and magnesium-based compounds are commercially available but rarely used. While these agents are effective at binding orally ingested phosphates, they vary in safety, potency and off-target effects, some of which may be salutary [e.g. low density lipoprotein (LDL) and uric acid lowering with sevelamer] and others adverse (low turnover bone disease and progressive vascular calcification with calcium) [8]. There remains a large unmet need for safe and effective phosphate binders with favorable off-target effects.

JTT-751 is a novel phosphate binder containing ferric citrate as an active ingredient [9, 10]. Ferric citrate is designated as a ‘Generally Recognized as Safe’ chemical by the USA Food and Drug Administration, and has been used as a food additive. JTT-751 has a larger surface area and faster dissolution rate than ferric citrate, and is expected to demonstrate efficacy as a phosphate binder [11]. The efficacy and safety of JTT-751 was demonstrated in a Phase 2 dose–response study in patients on hemodialysis with hyperphosphatemia [12].

The current study was a pivotal Phase 3 clinical trial designed to investigate the relative efficacy and safety of JTT-751 in patients on hemodialysis compared with sevelamer hydrochloride, a polymeric phosphate binder widely used to treat hyperphosphatemia in ESRD.

MATERIALS AND METHODS

Study design and oversight

This was a randomized, open-label, active controlled trial conducted across 49 centers in Japan. The study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice of the Japanese Ministerial Ordinance and was registered with the Japan Pharmaceutical Information Center as CTI-111433.

The study was sponsored by Japan Tobacco, Inc. The sponsor collected the trial data and analyzed the data according to a predefined statistical analysis plan. The authors interpreted the trial results and wrote the manuscript. The authors had access to the raw data.

Study population

Patients recruited were ≥20 years of age undergoing hemodialysis three times a week and had treated hemodialysis for ≥12 weeks prior to the initial screening date.

The inclusion criteria were as follows: (i) patients taking a constant dose of phosphate binders for 4 weeks prior to the initial screening date; (ii) patients who had discontinued phosphate binders with serum phosphate concentrations ≥1.97 mmol/L (6.1 mg/dL) and <3.23 mmol/L (10.0 mg/dL) and (iii) patients taking constant doses of vitamin D preparations, calcitonin preparations or cinacalcet (if applicable) for 4 weeks prior to the initial screening date.

The exclusion criteria were as follows: (i) patients with any gastrointestinal disease including acute peptic ulcers, chronic ulcerative colitis, regional enteritis, intestinal obstruction or dysphagia; (ii) patients with a history of gastrectomy or enterectomy; (iii) patients with marked constipation or severe gastrointestinal motility disorders; (iv) patients with hemochromatosis or serum ferritin concentrations >500 mg/mL or transferrin saturation (TSAT) >50% on the initial screening date; (v) patients with corrected serum calcium concentrations <2.00 mmol/L (8.0 mg/dL) or >2.75 mmol/L (11.0 mg/dL) at 1 week after the initial screening date; (vi) patients who had undergone parathyroidectomy or percutaneous ethanol injection therapy within 24 weeks prior to the initial screening date and (vii) patients with any history of
severe heart disease, hepatic dysfunction or hepatic cirrhosis as determined by the investigator.

**Intervention**

The current study comprised a 2-week screening and washout period and 12-week treatment period. After the initial screening date, any previously administered phosphate binders were discontinued. Patients with serum phosphate concentrations ≥1.97 mmol/L (6.1 mg/dL) and <3.23 mmol/L (10.0 mg/dL) at 1 week after the initial screening date were randomized in a 1:1 ratio to receive JTT-751 or sevelamer. Study drugs used were JTT-751 tablets, containing 250 mg of JTT-751 as anhydride and sevelamer hydrochloride tablets (Renagel®), containing 250 mg of sevelamer. These drugs were supplied by Japan Tobacco, Inc.

The starting dose was 1.5 g/day for JTT-751 and 3.0 g or 6.0 g/day for sevelamer [3.0 and 6.0 g/day were used if serum phosphate was <2.58 mmol/L (8.0 mg/dL) and ≥2.58 mmol/L (8.0 mg/dL), respectively, at 1 week after the initial screening date]. JTT-751 was administered orally three times daily immediately after each meal and sevelamer was administered orally three times daily immediately before each meal. The dose of JTT-751 was adjusted within the range of 1.5–6.0 g/day and the dose of sevelamer was adjusted within the range of 3.0–9.0 g/day. Dose titration criteria were established with reference to the target control range of serum phosphate recommended in the JSDT guidelines [3.5–6.0 mg/dL (1.13–1.94 mmol/L)]. Decisions for dose changes were made on Weeks 2, 4, 6 and 8. For JTT-751, the dose was increased by 2 tablets/dose if serum phosphate was ≥1.97 mmol/L (6.1 mg/dL) and decreased by 2 tablets/dose if serum phosphate was <1.13 mmol/L (3.5 mg/dL); for sevelamer, the dose was increased by 1 or 2 tablets/dose if serum phosphate was ≥1.97 mmol/L (6.1 mg/dL) and decreased by 1 or 2 tablets/dose if serum phosphate was <1.13 mmol/L (3.5 mg/dL), with these doses being maintained after this time.

Discontinuation criteria after the start of treatment with the investigational drugs were as follows: (i) ferritin ≥800 ng/mL; (ii) two consecutive serum phosphate concentrations <0.97 mmol/L (3.0 mg/dL) or ≥3.23 mmol/L (10.0 mg/dL) and (iii) two consecutive corrected serum calcium concentrations <1.88 mmol/L (7.5 mg/dL).

**Concomitant drugs and therapies**

During the study, concomitant use of drugs with phosphate-binding properties (e.g. magnesium- or aluminum-containing antacids, sucralfate) and other drugs that may affect phosphate absorption (e.g. niteritrol and colestimide) was prohibited. Dosages of vitamin D derivatives, calcitonin preparations, and cinacalcet were kept constant, except when they were changed to correct or prevent adverse events. Concurrent use of intravenous iron preparations was permitted when the investigator considered that iron-replacement therapy was necessary to treat ESRD-associated anemia.

From the initial screening date through to Week 12, or the observation day at the time of discontinuation, dietary recommendations and dialysis prescriptions were kept constant.

**Outcomes**

The primary outcome was the relative change (JTT-751 versus sevelamer) in serum phosphate concentrations from baseline to end of treatment. Secondary outcomes included the changes in corrected serum calcium and PTH concentrations from baseline to end of treatment. Corrected serum calcium concentrations were calculated according to Payne et al. [13]. Safety end points were adverse events, which were defined as changes in subjective symptoms or objective findings (e.g. blood pressure, pulse rate, body temperature, body weight, standard 12-lead electrocardiogram, laboratory tests) that were considered clinically significant. All adverse events were followed-up and recorded.

Iron-related tests [serum iron, ferritin, total iron-binding capacity (TIBC) and TSAT] and adherence were also assessed. Hematological tests were performed at SRL, Inc. (Tokyo, Japan) or at the participating institute and all other measurements were performed at SRL, Inc.

The volume normalized clearance × time product (Kt/V_{urea}) and body weight normalized protein catabolic rate (nPCR) were calculated to confirm stability in dietary intake and dialysis efficiency throughout the trial.

**Analytics**

Patients who received any investigational drug and who underwent efficacy assessments at Week 1 were included in the full analysis set. Patients who received any investigational drug and were assessed for safety end points were included in the safety analysis set.

We employed analysis of covariance with the treatment group as a factor and baseline value as a covariate to determine point estimates for differences in serum phosphate and calcium concentrations within and between groups. For PTH, we calculated within-group changes by determining the ratio in geometric means. We compared between-group changes in PTH using the non-parametric Wilcoxon rank sum test. We used Student’s t-test when comparing between-group changes in hemoglobin, hematocrit and electrolytes concentrations, and the Wilcoxon rank sum test when comparing between-group changes in iron-related tests and erythropoiesis-stimulating agent (ESA) dose. Two-tailed P-values <0.05 were considered statistically significant. We conducted statistical analyses using SAS (SAS System for Windows 9.2, Cary, NC, USA).

Safety end points were adverse events and adverse drug reactions. All adverse events were coded using MedDRA/V.13.1.

The rationale for sample size was as follows: using the non-inferiority margin of the mean relative difference in serum phosphate of 0.32 mmol/L (1.0 mg/dL), assuming that the mean treatment difference was 0.00 mmol/L (0.0 mg/dL) and the standard deviation of the change was 0.65 mmol/L (2.0 mg/dL), and considering the use of intra-individual dose titration in the study design, we calculated that a sample size of 100 patients per group was required to provide 90% power to show that the upper limit of the 95% CI for the mean treatment difference was below the non-inferiority margin. Adherence of JTT-751 through the trial period was calculated as the percentage of ingested tablets to total tablets prescribed.
RESULTS

Study participants
Figure 1 shows the patient disposition in this trial. Written informed consent was obtained from 427 patients. Of these, 230 patients met the inclusion criteria and were randomly assigned to JTT-751 (n = 116) or sevelamer (n = 114). After randomization, 229 patients received study treatment, all but one patient in the sevelamer group who withdrew consent. A total of 102 (88%) patients in the JTT-751 group and 97 (85%) patients in the sevelamer group completed the 12-week treatment. One hundred and fifteen (99%) patients in the JTT-751 group and 110 (96%) patients in the sevelamer group were included in the full analysis set population. There were no significant differences in baseline clinical characteristics between the groups (Table 1).

Throughout the study period, the mean prescribed dose was considerably lower in the JTT-751 group than in the sevelamer group. The percentage of patients achieving the target control range of serum phosphate [3.5−5.5 mmol/L (1.13−1.78 mmol/L)] recommended by the K/DOQI guidelines at the end of treatment was 62% in the JTT-751 group and 60% in the sevelamer group.

Efficacy
Efficacy parameters, measured at baseline and end of treatment, are presented in Table 2, and changes in serum phosphate, corrected serum calcium and intact PTH over time are shown in Figures 2 and 3.

At baseline, the serum phosphate concentrations in the JTT-751 and sevelamer groups were similar. Within both groups, serum phosphate concentrations at the end of treatment were significantly reduced from baseline (P < 0.001). The change in serum phosphate from baseline to end of treatment was −0.82 mmol/L (−2.53 mg/dL) in the JTT-751 group and −0.78 mmol/L (−2.40 mg/dL) in the sevelamer group. The least squares mean of the difference between the groups was −0.03 mmol/L (95% CI, −0.13 to 0.07 mmol/L) [−0.10 mg/dL (95% CI, −0.39 to 0.20 mg/dL)], establishing the non-inferiority of JTT-751.

The percentage of patients achieving the target control range of serum phosphate [3.5−5.5 mmol/L (1.13−1.78 mmol/L)] recommended by the K/DOQI guidelines at the end of treatment was 62% in the JTT-751 group and 60% in the sevelamer group.

The values of Kt/V urea and nPCR before and after the treatment with JTT-751 were similar to those for sevelamer (Table 2), suggesting that the relative efficacy in phosphate binding was not explained by changes in Kt/V and nPCR.

The changes in corrected serum calcium from baseline to end of treatment were 0.08 mmol/L (0.32 mg/dL) in the JTT-751 group and 0.04 mmol/L (0.15 mg/dL) in the sevelamer group (P < 0.001 in both groups). Although a statistically significant difference was observed between groups (P = 0.01), the relative change was not considered clinically meaningful.

Intact PTH concentrations at the end of treatment were significantly reduced from baseline in both groups (P < 0.001). The ratio of the geometric mean at the end of treatment to baseline was 0.74 in the JTT-751 group and 0.73 in the sevelamer group. There was no significant difference in the change in PTH between the groups (P = 0.73).

Safety
A total of 229 treated patients were included in the safety analysis set. No deaths were observed during the study. Six serious adverse events occurred among the 116 patients in the JTT-751 group (5.2%), compared with three serious adverse events among the 113 patients in the sevelamer group (2.7%). All of these events were considered to be unrelated to study treatments (Table 3).

A total of five of the 116 patients in the JTT-751 group (4.3%) reported five adverse events (excluding serious adverse events) that led to discontinuation of study treatment. In comparison, three adverse events (excluding serious adverse events) led to discontinuation of study treatment in 3 of the 113 patients in the sevelamer group (2.7%). All of these adverse events were considered to be related to study treatment.

A total of 192 adverse events occurred in 85 (73%) of the 116 patients in the JTT-751 group, while 170 adverse events occurred in 83 (74%) of the 113 patients in the sevelamer group. None of these events were considered to be severe and most were considered to be mild. Gastrointestinal disorders were the most commonly observed adverse events by system organ classes (SOC) and occurred in 43 patients in the JTT-751 group (37%) and 39 patients in the sevelamer group (35%).
A total of 35 adverse drug reactions occurred in 29 (25%) of the 116 patients in the JTT-751 group and 36 adverse drug reactions occurred in 32 (28%) of the 113 patients in the sevelamer group. The most frequent adverse drug reaction was diarrhea (12 patients, 10%) in the JTT-751 group and constipation (21 patients, 19%) in the sevelamer group. The incidences of adverse events and adverse drug reactions did not differ between the groups. Furthermore, most of the observed adverse drug reactions were considered to be mild.

With respect to laboratory parameters, significant relative differences in mean serum chloride concentrations were observed, as were corresponding relative changes in serum bicarbonate (P < 0.001 for both comparisons; Table 4).

Finally, small but statistically significant relative increases in mean hemoglobin and hematocrit were observed (P < 0.001), with both rising significantly in the JTT-751 group (P < 0.001; Table 4).

**Iron-related tests and ESA dosing**

Table 4 shows the changes in iron-related parameters (serum iron, ferritin, TIBC, TSAT) in both groups. Relative results were significantly different for all parameters. Figure 4 shows the changes in serum ferritin over time. In the JTT-751 group, the median weekly ESA dose declined from baseline 4500 IU (interquartile range: 3000, 6000; n = 59) to end of treatment 3000 IU (interquartile range: 1500, 4500; n = 57) for recombinant erythropoietin product and declined from baseline 12.50 μg (interquartile range: 10.00, 30.00; n = 40) to end of treatment 10.00 μg (interquartile range: 5.00, 15.00; n = 42) for darbepoetin alpha. There were no obvious differences in ESA use in the sevelamer group. Relative to the sevelamer group, ESA dose tended to decrease with JTT-751 treatment (recombinant erythropoietin product; P = 0.09, darbepoetin alpha; P < 0.001).

**DISCUSSION**

The present study was a multicenter, randomized, open-label trial, designed to investigate the relative efficacy and safety of JTT-751 in Japanese patients undergoing maintenance hemodialysis, compared with the global standard non-calcium-based phosphate binder, sevelamer. Sevelamer hydrochloride was chosen as the control treatment because it was available in Japan.
Serum phosphate concentrations declined in both groups, with the relative decline slightly but not significantly larger in the JTT-751 group, demonstrating non-inferiority relative to sevelamer. Relative changes in corrected serum calcium and PTH were similar in both groups. Sevelamer hydrochloride led to relative metabolic acidosis and lowered LDL cholesterol, findings previously reported with sevelamer [14, 15], while JTT-751 led to higher hemoglobin and hematocrit, serum ferritin and TSAT.

### Table 2. Efficacy parameter values, Kt/V and nPCR (FAS analysis population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>JTT-751 (n = 115)</th>
<th>Sevelamer (n = 110)</th>
<th>Between-group difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (mmol/L)</td>
<td>2.53 ± 0.39</td>
<td>1.72 ± 0.40</td>
<td>−0.82 (−0.92, −0.72)</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ca (mmol/L)</td>
<td>2.21 ± 0.13</td>
<td>2.29 ± 0.16</td>
<td>0.08 (0.05, 0.11)</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>i-PTH (pg/mL)</td>
<td>230.0 (150.0, 331.0)</td>
<td>177.0 (108.0, 271.0)</td>
<td>0.74 (0.68, 0.81)</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.51 ± 0.29</td>
<td>1.51 ± 0.28</td>
<td>0.00 ± 0.11 (−0.02, 0.02)</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
<td>0.91 ± 0.15</td>
<td>0.89 ± 0.15</td>
<td>−0.02 ± 0.12 (−0.05, 0.00)</td>
<td>0.05&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

BL, baseline (the day of start of treatment); EOT, end of treatment (Week 12 or the observation day of the time of discontinuation); P, phosphate; Ca, calcium; i-PTH, intact parathyroid hormone. Data are expressed as mean ± SD, except for i-PTH values, which are expressed as median (25th and 75th percentile).

<sup>a</sup>For changes in i-PTH, values are expressed as ratio of geometric mean (95% confidence interval).

<sup>b</sup>Values of between-group differences are expressed as least squares mean difference (95% confidence interval), except for i-PTH values.

<sup>c</sup>Paired t-test.

<sup>d</sup>ANCOVA (analysis of covariance) model.

<sup>e</sup>Wilcoxon rank sum test, change in i-PTH.

<sup>f</sup>t-test.
The most commonly observed adverse drug reaction was diarrhea in the JTT-751 group, while the most common adverse drug reaction with sevelamer was constipation, which has previously been reported with sevelamer [14]. In conclusion, the results of the current study demonstrate safety and efficacy with regard to the targeted adverse events in the JTT-751 group, as well as non-inferiority in terms of efficacy relative to sevelamer hydrochloride. In addition, JTT-751 might have the ability to replenish iron stores and reduce ESA dose. Longer term trials of JTT-751 will help to clarify its relative efficacy and safety and refine the population(s) of patients best suited for its use.

Table 3. Summary of adverse events (safety population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>JTT-751 (n = 116)</th>
<th>Sevelamer (n = 113)</th>
<th>Between-group difference, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>85 (72.3)</td>
<td>83 (73.5)</td>
<td>0.8102</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>6 (5.2)</td>
<td>3 (2.7)</td>
<td>0.5329</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>5 (4.3)</td>
<td>3 (2.7)</td>
<td>0.5329</td>
</tr>
<tr>
<td>Any adverse drug reaction</td>
<td>29 (25.0)</td>
<td>32 (28.3)</td>
<td>0.3854</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (10.3)</td>
<td>1 (0.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3 (2.6)</td>
<td>4 (3.5)</td>
<td>0.6064</td>
</tr>
<tr>
<td>Hemoglobin increased</td>
<td>4 (3.4)</td>
<td>0</td>
<td>0.0025</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (3.4)</td>
<td>21 (18.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2 (1.7)</td>
<td>4 (3.5)</td>
<td>0.6064</td>
</tr>
</tbody>
</table>

aMedDRA version 13.1 preferred terms. Values are numbers of patients (%).
bFive adverse events (including SAEs) (hemoglobin increased in three patients and diarrhea in two patients) that led to discontinuation of JTT-751 treatment occurred in the JTT-751 group. In comparison, three adverse events (including SAEs) (abdominal pain and pruritus: each in 1 subject) led to discontinuation of sevelamer treatment in the sevelamer group.
cAdverse drug reactions occurring in ≥ 2 patients in either treatment group are listed.

Table 4. Special clinical laboratory evaluations (safety analysis population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>JTT-751 (n = 116)</th>
<th>Sevelamer (n = 113)</th>
<th>Between-group difference, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (μg/dL)</td>
<td>52.5 (43.0, 68.0)</td>
<td>81.5 (63.0, 96.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>48.2 (18.8, 110.0)</td>
<td>123.0 (56.6, 223.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TIBC (μg/dL)</td>
<td>249.0 (219.5, 286.0)</td>
<td>226.5 (200.5, 247.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>23.0 (17.0, 28.2)</td>
<td>35.9 (29.0, 43.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
<td>101.4 ± 3.1</td>
<td>101.5 ± 3.4</td>
<td>0.6435*</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>17.1 ± 2.8</td>
<td>18.6 ± 2.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.9 ± 1.0</td>
<td>11.8 ± 1.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>33.5 ± 3.3</td>
<td>36.1 ± 4.7</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

aWilcoxon signed rank test.
bWilcoxon rank sum test.
cPaired t-test.
dUnpaired t-test.

BL, baseline (the day of the start of treatment); EOT, end of treatment (Week 12 or the observation day at the time of discontinuation); Hb, hemoglobin; TIBC, total iron-binding capacity; TSAT, transferring saturation. Data are expressed as mean ± SD, except for serum iron, ferritin, TIBC and TSAT, which are expressed as median (25th and 75th percentile).

Table 5. Summary of adverse events (safety population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>JTT-751</th>
<th>Sevelamer</th>
<th>Between-group difference, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal distension</td>
<td>5 (4.3)</td>
<td>3 (2.7)</td>
<td>0.5329</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (3.4)</td>
<td>21 (18.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemoglobin increased</td>
<td>3 (2.6)</td>
<td>4 (3.5)</td>
<td>0.6064</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (3.4)</td>
<td>0</td>
<td>0.0025</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (3.4)</td>
<td>1 (0.9)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (1.7)</td>
<td>4 (3.5)</td>
<td>0.6064</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

aMedDRA version 13.1 preferred terms. Values are numbers of patients (%).

Table 6. Special clinical laboratory evaluations (safety analysis population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>JTT-751</th>
<th>Sevelamer</th>
<th>Between-group difference, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (μg/dL)</td>
<td>52.5 (43.0, 68.0)</td>
<td>81.5 (63.0, 96.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>48.2 (18.8, 110.0)</td>
<td>123.0 (56.6, 223.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TIBC (μg/dL)</td>
<td>249.0 (219.5, 286.0)</td>
<td>226.5 (200.5, 247.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>23.0 (17.0, 28.2)</td>
<td>35.9 (29.0, 43.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
<td>101.4 ± 3.1</td>
<td>101.5 ± 3.4</td>
<td>0.6435*</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>17.1 ± 2.8</td>
<td>18.6 ± 2.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.9 ± 1.0</td>
<td>11.8 ± 1.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>33.5 ± 3.3</td>
<td>36.1 ± 4.7</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

aWilcoxon signed rank test.
bWilcoxon rank sum test.
cPaired t-test.
dUnpaired t-test.

BL, baseline (the day of the start of treatment); EOT, end of treatment (Week 12 or the observation day at the time of discontinuation); Hb, hemoglobin; TIBC, total iron-binding capacity; TSAT, transferring saturation. Data are expressed as mean ± SD, except for serum iron, ferritin, TIBC and TSAT, which are expressed as median (25th and 75th percentile).
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CONFLICT OF INTEREST STATEMENT

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REFERENCES


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