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Effect of switching from cinacalcet to etelcalcetide on secondary hyperparathyroidism in patients undergoing hemodialysis: an ESCORT trial

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Abstract

Background: Etelcalcetide is the first intravenously administered calcimimetic agent used to manage secondary hyperparathyroidism (SHPT) in hemodialysis (HD) patients. We evaluated the safety and efficacy of replacing cinacalcet with etelcalcetide in HD patients.

Methods: One hundred and thirty-three patients HD on cinacalcet were screened, and 93 patients with serum-intact parathyroid hormone (iPTH) level of ≥ 60 pg/mL and serum albumin-corrected calcium (cCa) level of ≥ 8.4 mg/dL were enrolled. The patients were divided into three groups based on the dose of cinacalcet (i.e., 25, 50, and ≥ 75 mg) and switched to etelcalcetide. Etelcalcetide was administered three times per week for 24 weeks. The primary and secondary endpoints were etelcalcetide conversion dose and etelcalcetide effectiveness for iPTH levels (target range: 60–240 pg/mL), respectively.

Results: Of the 68 patients whose iPTH level was within the management target at screening, 60 patients maintained the target level at the end of the study. Among patients whose iPTH level exceeded 240 pg/mL at screening, it decreased from 401 ± 246 pg/mL to 220 ± 209 pg/mL ($p < 0.001$) at the end of the study. Among 22 patients with the iPTH level of ≥ 240 pg/mL, 17 achieved the target level. The mean dose of cinacalcet was 41.4 ± 22.2 mg/day and that of etelcalcetide at the end of the study was 6.4 ± 3.7 mg/session in all patients. In 45 patients whose iPTH level was within the management target throughout the study and active vitamin D agent and calcium-based phosphate binder doses were constant, the mean dose of cinacalcet was 45.0 ± 22.4 mg/day and that of etelcalcetide at the end of the study was 6.1 ± 3.1 mg/session. The spKt/V might affect the ratio of etelcalcetide per session to oral cinacalcet per day (45 patients, $p = 0.087$; 90 patients, $p < 0.05$) in the generalized linear model. Etelcalcetide-induced severe adverse events were not observed.

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Conclusions: This study reports the conversion dose of etelcalcetide and demonstrates its safety and efficacy in HD patients with SHPT previously treated with cinacalcet.

Trial registration: UMIN, [UMIN000027637](https://clinicaltrials.gov/ct2/show/study?term=UMIN000027637); Registered on June 5, 2017.

Keywords: Cinacalcet, Etelcalcetide, Hemodialysis, Intact-PTH, Secondary hyperparathyroidism

Background

Secondary hyperparathyroidism (SHPT), a serious hemodialysis (HD) complication, causes bone lesions such as osteitis fibrosa and increases vascular calcification to life-threatening levels [1]. Previous observational studies in patients undergoing dialysis correlated elevated serum levels of phosphorus (P), calcium (Ca), parathyroid hormone (iPTH), and fibroblast growth factor 23 (FGF-23) with death and cardiovascular events [2, 3]. At the end of 2012, the proportion of patients with HD whose Ca (8.4–10.0 mg/dL), P (3.5–6.0 mg/dL), and iPTH (60–240 pg/dL) levels were within the target ranges according to the Japanese Clinical Guidelines was 33.1% in Japan [4]. Moreover, several patients with bone and mineral metabolism markers outside the range recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI) have been reported [5].

Elevated serum iPTH level stimulates bone resorption, thereby releasing Ca and P and leading to not only bone and mineral metabolism-related diseases but also vascular calcification [6], which are strongly associated with increased morbidity and mortality in patients with HD [3, 7, 8]. Thus, the management of iPTH within an appropriate range is important.

Currently, the treatments for SHPT include active vitamin D agents and calcimimetics. The emergence of calcimimetics has led to advances in SHPT treatment. Since 2004, cinacalcet has been marketed in the USA, and this has improved the conformance rate of K/DOQI management target for iPTH, Ca, and P in HD patients with SHPT [9, 10]. Furthermore, despite the beneficial clinical effects of cinacalcet, its use has been limited by gastrointestinal adverse events, including nausea and vomiting. Furthermore, most patients with SHPT require other oral medications to treat associated complications, resulting in poor adherence.

Etelcalcetide, the first intravenously administered calcimimetic agent, substantially reduces the iPTH level, with only a few gastrointestinal symptoms [11–13]. Furthermore, studies have reported relatively few drug interactions and long-term iPTH suppression with etelcalcetide [14, 15]. Moreover, Block GA et al. showed that etelcalcetide is not superior to cinacalcet in terms of gastrointestinal adverse effects and substantially reduces iPTH levels [16]. Owing to the reduced efficacy and

adherence of cinacalcet compared with etelcalcetide, switching to etelcalcetide may be more beneficial to patients with a high iPTH level.

There are only a few studies on the benefits of etelcalcetide in CKD-mineral and bone disorder (CKD-MBD), its equivalent converted amounts, and its safety after switching from cinacalcet. Therefore, we conducted a prospective study to determine etelcalcetide conversion dose and assess the safety and efficacy of replacing cinacalcet with etelcalcetide in HD patients with SHPT.

Methods

Patients

This was a multicenter open-labeled study. Japanese HD patients with SHPT (aged > 20 years) were enrolled. The major inclusion criteria were over 24 weeks of cinacalcet treatment, at least 3 months of fixed-dose administration before screening, no change in phosphate binder or activated vitamin D dosage within 14 days before screening, and no change in dialysis procedure or hemodialysis instrument within 14 days before screening. The spKt/V was more than 1.2. The major exclusion criteria were as follows: serum-corrected calcium (cCa) level of < 8.4 mg/dL at screening, primary hyperparathyroidism; scheduled parathyroidectomy, parathyroid intervention, or kidney transplant during the study period; serum iPTH level of < 60 pg/mL; poor compliance of cinacalcet; and pregnancy, possibility or plan of pregnancy, and lactation.

This multicenter open-labeled study was conducted in compliance with the International Council for Harmonization (ICH)—Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the institutional review boards of Kurume University School of Medicine (No: 17001), Yame General Hospital (No: 17-001), Moriyama Clinic of Internal Medicine, Nagata Hospital, Sugi Cardiovascular Hospital, Yamaguchi Saiseikai General Hospital, Wada Cardiovascular Clinic, Usui Clinic, Chiba Naika Jyunkankika, and Miyazakinaika Medical Clinic: Clinical Research Network Fukuoka (No: 17-E06). Written informed consent was obtained from each study site. Furthermore, written informed consent was obtained from all patients before enrollment. This study was funded by Ono Pharmaceutical Co., Ltd (Osaka, Japan).

Study procedure

We divided the patients into three groups according to the oral dose of cinacalcet (25, 50, and ≥ 75 mg/day) and switched to etelcalcetide. Etelcalcetide was administered within 7 days of the last cinacalcet dose and three times per week for 24 weeks. As a starting dose, 5 mg/session etelcalcetide was administered three times a week. The dose was then appropriately adjusted within the range of 2.5–15 mg/session, three times a week; iPTH and cCa levels of the patients were monitored. The administration period was set to 6 months (Fig. 1). Varying criteria were used for etelcalcetide dosing. The same dose of etelcalcetide was maintained for over 4 weeks; if the iPTH level was > 240 pg/mL and cCa level was ≥ 8.4 mg/dL, the etelcalcetide dose was increased at a rate of 2.5–5.0 mg. If the iPTH level was < 60 pg/mL or cCa level was < 8.4 mg/dL, the dose of etelcalcetide was reduced and treatment with active vitamin D agent and calcium-based phosphate binders (CBPBs) was stopped or adjusted. Other phosphate binders were adjusted to reach the target level of serum P (3.5–6.0 mg/dL). The dose adjustment of each medication was left to the discretion of the prescribing physician.

Biochemical and other determinations

A blood test was performed at the start of dialysis and after 2 days without dialysis. A blood biochemistry test including iPTH and serum cCa was performed at screening and at the end of the study. iPTH and serum P levels were measured once every 2 weeks, from the start of the study to week 12, and once every 4 weeks after week 12. Serum cCa level was measured every week until week 12, and every 2 weeks after week 12 (Fig. 1). As an exploratory study, FGF-23, bone alkaline phosphatase (BAP), and tartrate-resistant acid phosphatase (TRACP-5b) were measured at screening and at the end of the study. These analyses were performed at the

Special Reference Laboratory (Tokyo, Japan). Serum iPTH level was determined using the electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Tokyo, Japan) (reference range, 10–65 pg/ml). FGF-23 was measured using the enzyme-linked immunosorbent assay kit (Kainos, Tokyo, Japan) (reference range, 14.7–40.5 pg/mL), BAP using the chemiluminescence enzyme immunoassay (Access Ostase, Beckman Coulter, Tokyo, Japan) (reference range, 3.7–20.9 µg/L), and TRACP-5b using the enzyme immunoassay (Osteolinks TRAP-5b, Nittobo Medical, Fukushima, Japan) (reference range, 170–590 mU/dL for men and 120–420 mU/dL for women). cCa level was calculated using the Payne formula [17].

Endpoints

The primary endpoints were etelcalcetide dose change and cinacalcet to etelcalcetide conversion safety. To analyze the dose changes in the cinacalcet groups (25, 50, and ≥ 75 mg), we analyzed etelcalcetide dose variations. In addition, we assessed the relationship of the ratio of etelcalcetide per session to oral cinacalcet per day with clinical factors. Adverse events (AEs) were also recorded. The secondary endpoint was the effectiveness of etelcalcetide, evaluated using the number of patients with iPTH level in the target range of 60–240 pg/mL. We used the iPTH target range 60–240 pg/mL as proposed by the Japanese Society for Dialysis Therapy [18]. During the transition, we also analyzed FGF-23 and bone metabolism markers.

Statistical analysis

Data are presented as mean ± standard deviation (SD). The efficacy of switching from cinacalcet to etelcalcetide was evaluated using the iPTH level and other clinical measures, based on Wilcoxon signed-rank test. To compare the baseline characteristics of patients among each group, an analysis of variance or Fisher’s exact test was

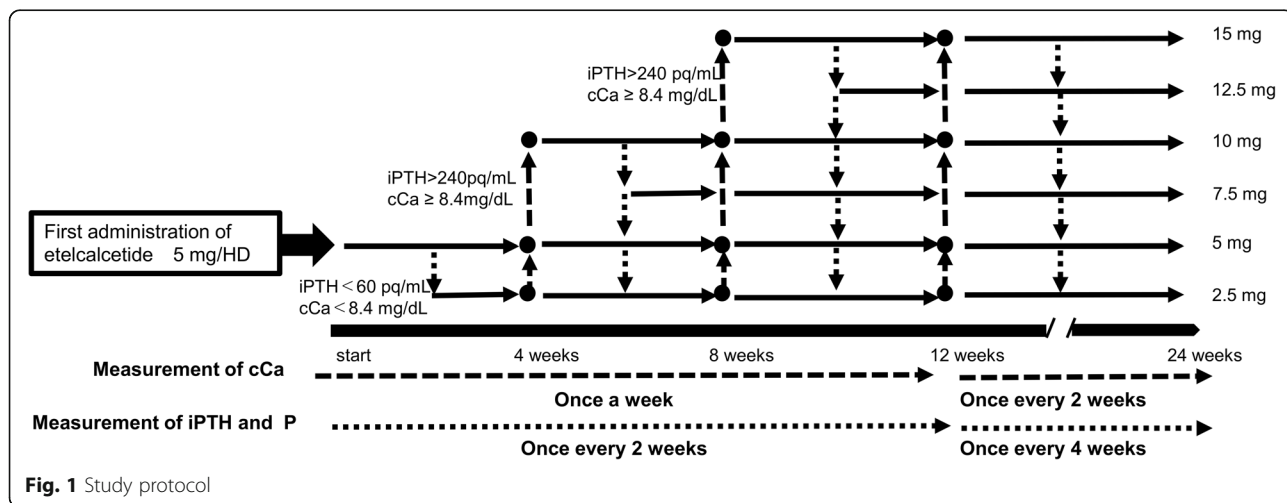
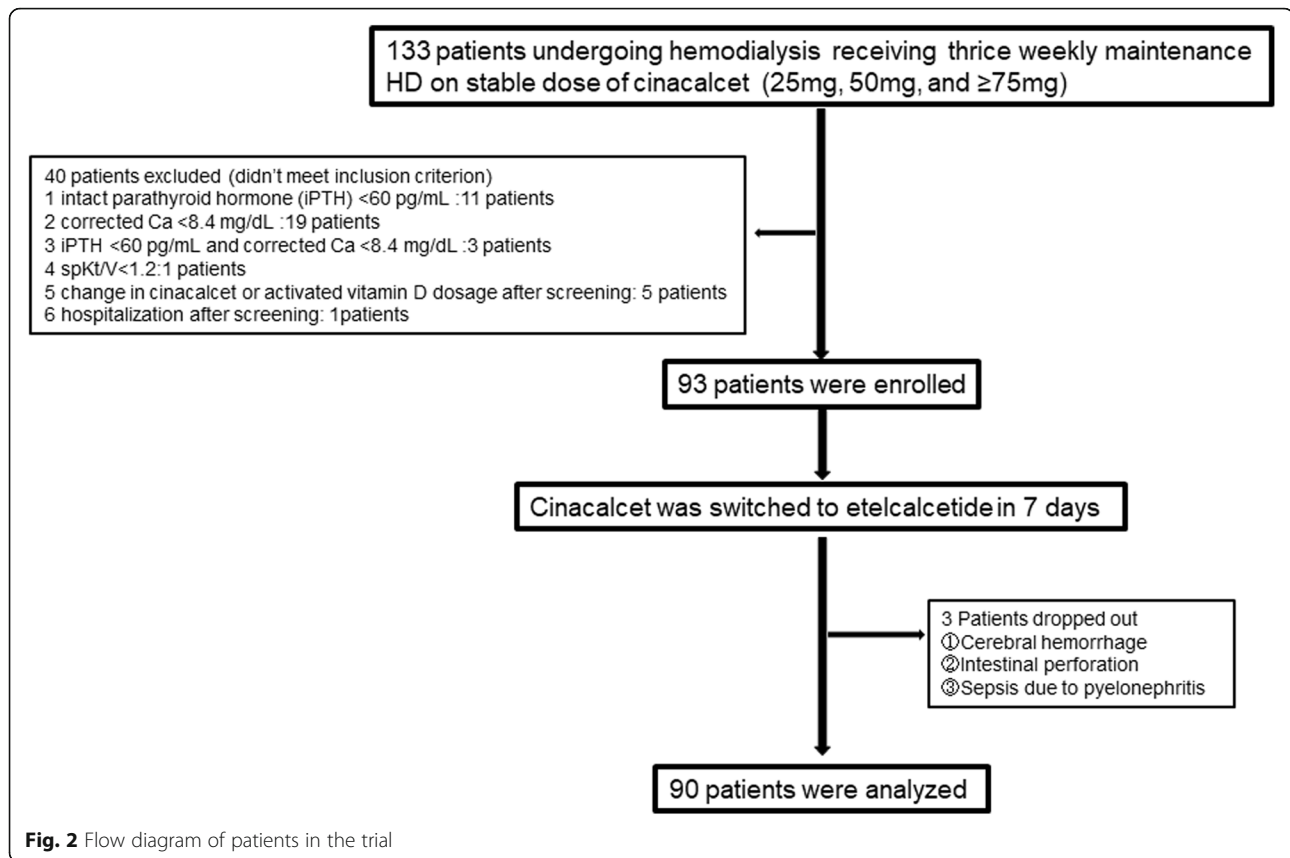


Fig. 1 Study protocol



performed. To determine the independent variables of etelcalcetide per session to oral cinacalcet per day, we performed a generalized linear model including sex and age, duration of dialysis, spKt/V, cCa, P, and iPTH. Results with a p value of < 0.05 were considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient enrollment

Patients were enrolled between June 2017 and June 2018. Of the 133 patients, 40 were excluded at screening (cCa < 8.4 mg/dL, 19 patients; iPTH < 60 pg/mL, 11 patients; cCa < 8.4 mg/dL and iPTH < 60 pg/mL, 3 patients; spKt/V < 1.2 , 1 patient; change in cinacalcet or activated vitamin D dosage after screening, 5 patients, hospitalization

Table 1 Demographic and baseline characteristics of the study patients

Cinacalcet dose before switching	25 mg/day (n = 53)	50 mg/day (n = 18)	≥ 75 mg/day (n = 19)	Total (n = 90)	P value
Female (%)	16 (30.2)	3 (16.7)	8 (42.1)	27 (30.0)	$P = 0.227$
Age (year)	63.6 ± 8.7	61.6 ± 13.1	57.8 ± 10.8	62.0 ± 10.3	$P = 0.106$
Dry weight (kg)	59.2 ± 11.7	63.6 ± 17.4	58.7 ± 11.3	60.0 ± 12.9	$P = 0.414$
Systolic blood pressure (mmHg)	148.7 ± 25.0	144.8 ± 22.3	144.5 ± 18.0	147.0 ± 23.0	$P = 0.717$
Duration of dialysis (years)	15.1 ± 8.0	13.0 ± 6.7	16.5 ± 7.1	15.0 ± 7.6	$P = 0.356$
spKt/V	1.7 ± 0.3	1.6 ± 0.3	1.7 ± 0.2	1.7 ± 0.3	$P = 0.540$
cCa (mg/dL)	8.97 ± 0.40	9.07 ± 0.56	9.24 ± 0.41	9.05 ± 0.45	$P = 0.074$
Phosphate (mg/dL)	5.18 ± 1.09	5.64 ± 1.00	5.48 ± 1.34	5.34 ± 1.13	$P = 0.272$
Intact PTH (pg/mL)	180 ± 97	177 ± 123	289 ± 301	202 ± 170	$P = 0.040$
Alb (g/dL)	3.7 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	$P = 0.317$
Mg (mg/dL)	2.0 ± 0.3	2.6 ± 0.4	2.6 ± 0.3	2.5 ± 0.4	$P = 0.106$

cCa corrected calcium, Intact PTH Intact parathyroid hormone, Alb albumin, Mg magnesium

after screening, 1 patient). Of the remaining 93 patients, three withdrew due to serious AEs and 90 completed the study (Fig. 2).

Clinical characteristics of the patients

Clinical data of the patients obtained at screening are presented in Table 1. We enrolled 63 men and 27 women aged 62.0 ± 10.3 years, who underwent dialysis for 15.0 ± 7.6 years. Oral cinacalcet at doses of 25, 50, and ≥ 75 mg/day was previously administered to 53, 18, and 19 (75 mg ($n = 16$), 100 mg ($n = 3$)) patients, respectively. In an ongoing medication compliance questionnaire survey, 80 patients indicated that they took the required dose of medication almost daily (6–7 days a week), 10 patients admitted that they sometimes forgot (4–6 days a week), and none of the patients acknowledged that they frequently forgot (2–3 days a week) or hardly remembered (0–1 day a week). Therefore, the study population exhibited a relatively favorable medication adherence.

Laboratory analysis

iPTH, serum cCa, and serum P variations in the enrolled patients are shown in Fig. 3. Throughout the study, the iPTH level decreased from 202 ± 169 pg/mL to 166 ± 119 pg/mL ($p = 0.051$), particularly in the 25 mg group ($p = 0.005$). The serum cCa level decreased from 9.05 ± 0.45 mg/dL to 8.74 ± 0.52 mg/dL ($p < 0.001$), especially in the 25 mg and ≥ 75 mg groups ($p < 0.001$, $p = 0.002$, respectively). The serum P level showed no significant change (5.34 ± 1.13 mg/dL to 5.23 ± 1.33 mg/dL) ($p = 0.314$).

The iPTH level in some patients (68) was 60–240 pg/mL at screening, whereas that in some patients (22) exceeded 240 pg/mL. These 68 patients showed no significant change in the iPTH level (from 138 ± 47 pg/mL at screening to 149 ± 63 pg/mL) ($p = 0.106$; Fig. 4); 60 (88.2%) maintained the target level (60–240 pg/mL), 5 exceeded 240 pg/mL, and 3 dropped below 60 pg/mL (Table 2).

In the 22 patients with the iPTH level of 240 pg/mL at screening, the iPTH level significantly decreased from 401 ± 246 pg/mL to 220 ± 209 pg/mL ($p < 0.001$) (Fig. 4). In 17 (77.3%) patients, the target iPTH level was achieved, and in 5 patients, the iPTH level remained above 240 pg/mL (Table 2).

Etelcalcetide dose changes

In 45/90 patients (25 mg: $n = 22$, 50 mg: $n = 11$, ≥ 75 mg: $n = 12$), the iPTH level was within the target (60–240 pg/mL) throughout the study, and the doses of active vitamin D and CBPBs were the same before and after the study. In these 45 patients, the mean dose of cinacalcet was 45.0 ± 22.4 mg/day and that of etelcalcetide was 6.1 ± 3.1 mg/session, at the end of the study. The ratio

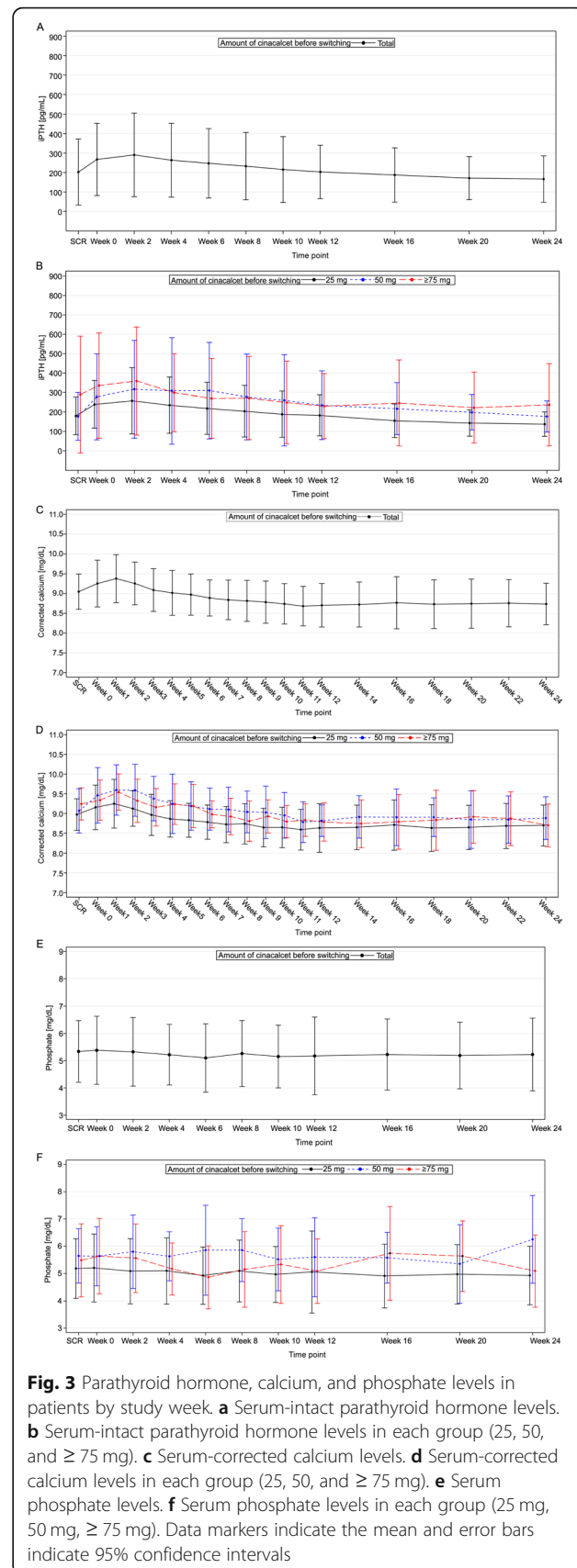
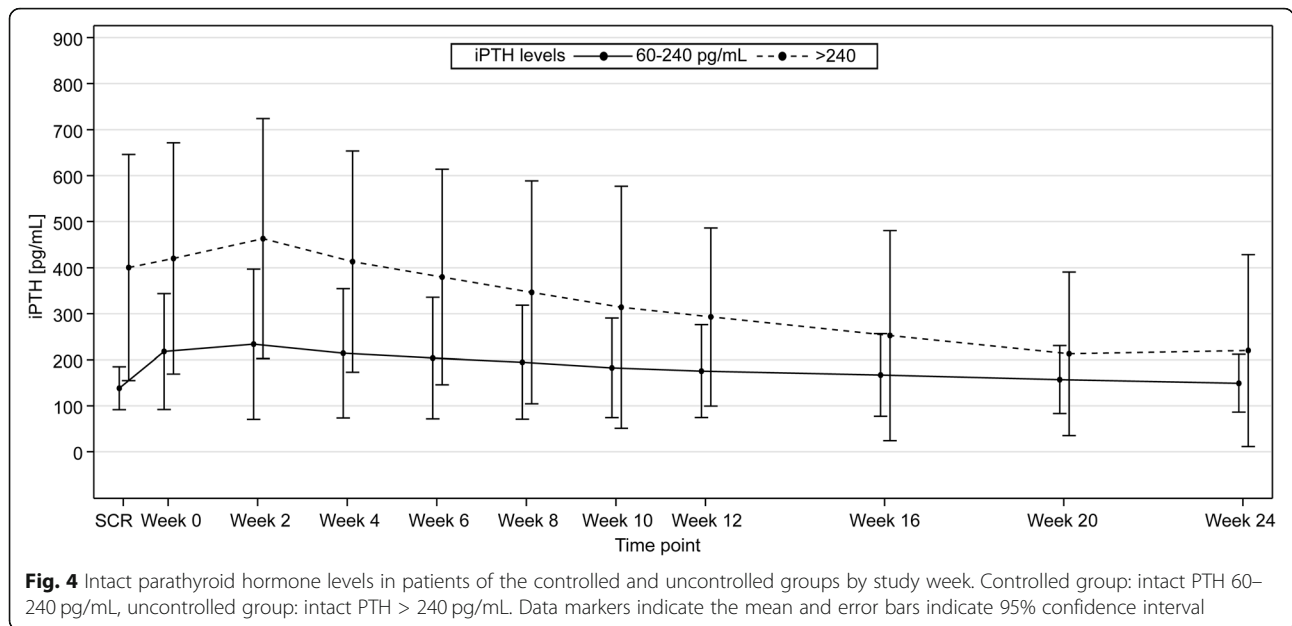


Fig. 3 Parathyroid hormone, calcium, and phosphate levels in patients by study week. **a** Serum-intact parathyroid hormone levels. **b** Serum-intact parathyroid hormone levels in each group (25, 50, and ≥ 75 mg). **c** Serum-corrected calcium levels. **d** Serum-corrected calcium levels in each group (25, 50, and ≥ 75 mg). **e** Serum phosphate levels. **f** Serum phosphate levels in each group (25 mg, 50 mg, ≥ 75 mg). Data markers indicate the mean and error bars indicate 95% confidence intervals



of etelcalcetide per session to oral cinacalcet per day was approximately 0.16 ± 0.09 . When the $spKt/V$ increased by 1.0, the ratio of etelcalcetide per session to oral cinacalcet per day tended to increase by 0.54 ($p = 0.087$) in these 45 patients (Table 3). For the 45 patients, in the 25 mg group, the starting dose was 5 mg/session, which was temporarily reduced to 4.7 ± 0.9 mg/session at week 4 and increased to 5.2 ± 2.3 mg/session at week 24 (Fig. 5). In the 50 mg group, a dose of 5 mg/session was maintained until week 4 and increased to 5.5 ± 1.9 mg/session from week 6 (Fig. 5). In ≥ 75 mg group, the dose was gradually increased from 5 mg/session to 8.1 ± 4.3 mg/session at week 24 (Fig. 5). In the 25 mg group, the dose was 5 mg/session in 13/22 (59.1 %) patients; the dose was reduced in 5 (22.7 %) and increased in 4 (18.2 %) patients. In the 50 mg group, the dose was maintained at 5 mg/session in 8 of 11 (72.7 %) patients, reduced in one (9.1 %), and increased in 2 (18.2 %) patients. In the group of patients taking ≥ 75 mg, the dose of 5 mg/session was maintained in 6/12 (50 %) patients and increased in 6 (50 %) patients (Table 4). In 90 patients, the mean dose of cinacalcet was 41.4 ± 22.2 mg/day and that of etelcalcetide was 6.4 ± 3.7 mg/session; the ratio of etelcalcetide per session

to oral cinacalcet per day was approximately 0.18 ± 0.12 , at the end of the study. When the $spKt/V$ increased by 1.0, the ratio of etelcalcetide per session to oral cinacalcet per day increased by 0.58 ($p < 0.05$) in 90 patients (Table 3).

Changes in the doses of medications

Active vitamin D was used in 83/90 patients, which increased to 85/90 at week 24, and the dose was increased in 20 and decreased in 7 patients. CBPBs were used in 46/90 patients, which increased to 48/90 at week 24, and the dose was increased in 9 and decreased in 4 patients. The dose changes for the other phosphate binders are presented in Table 5.

Exploratory endpoints

FGF-23 significantly decreased from 9115 ± 11435 pg/mL to 7591 ± 9322 pg/mL at week 24 ($p = 0.009$). Furthermore, both BAP and TRACP-5b significantly decreased (16.0 ± 7.0 μ g/L vs. 13.8 ± 5.8 μ g/L ($p < 0.001$) and 580 ± 292 mU/dL vs. 405 ± 229 mU/dL ($p < 0.001$), respectively) (Supplementary Table 1).

Adverse events

AEs were observed in 51/93 patients when cinacalcet was switched to etelcalcetide. Three patients experienced mild AEs associated with etelcalcetide during the study. All AEs were mild (Table 6). There were no new gastrointestinal symptoms associated with etelcalcetide. The AEs in three patients who dropped out of the study (cerebral hemorrhage, sepsis, and small intestinal perforation) were not related to etelcalcetide. AEs unrelated to

Table 2 Distribution of intact PTH before and after the study ($n = 90$)

iPTH before switching	iPTH at week 24 after switching			Total
	< 60 pg/mL	60–240 pg/mL	> 240 pg/mL	
60–240 pg/mL	3	60	5	68
> 240 pg/mL	0	17	5	22
Total	3	77	10	90

Table 3 The relationship of the ratio of etelcalcetide per session to oral cinacalcet per day with clinical factors

	45 patients		90 patients	
	Exp (estimate)	p value	Exp (estimate)	p value
Age	1.02	0.919	1.08	0.642
Sex	1.01	0.199	1.01	0.071
Duration of dialysis	0.74	0.147	0.81	0.221
spKt/V	0.54	0.087	0.58	< 0.05
cCa	1.00	0.989	0.96	0.779
P	1.01	0.904	0.97	0.642
iPTH	1.00	0.909	1.00	0.674

45 patients with intact PTH levels within the management target at screening and at the end of the study and with constant vitamin D agent and calcium-based phosphate binder doses

the medications ($\geq 5\%$) included shunt problems (20.4%), cold (20.4%), and lower back pain (6.5%). During the study, the cCa level was < 8.4 mg/dL in 50 (55.6%) patients (25 mg: $n = 33$, 50 mg: $n = 8$, and ≥ 75 mg: $n = 9$); among them, the cCa level was < 7.5 mg/dL in seven patients (7.8%) (25 mg: $n = 4$, 50 mg: $n = 1$, and ≥ 75 mg: $n = 2$). However, all cases were controlled with etelcalcetide dose reduction and treatment with active vitamin D and CBPBs. Etelcalcetide treatment was ceased in one patient, because the iPTH level decreased below 60 pg/mL.

Discussion

In this ESCORT trial, we aimed to determine the conversion dose of etelcalcetide and assess its safety and efficacy in HD patients with SHPT previously treated with cinacalcet.

A head-to-head study, in which cinacalcet 51.4 mg/day was switched to etelcalcetide 5 mg/session, reported a slightly stronger effect for etelcalcetide [16]. Xipell et al. suggested the following conversion formula for etelcalcetide mg/session = $0.111 \times$ cinacalcet mg/day + 0.96. Unlike a previous study [19], we analyzed dose conversion in 45 patients with iPTH levels maintained between 60 and 240 pg/mL throughout the study period and maintained constant doses of active vitamin D and CBPBs. Consequently, our study could provide a more accurate conversion of cinacalcet and etelcalcetide than previous studies. Cinacalcet was administered at a dose of 45.0 ± 22.4 mg/day to these 45 patients before etelcalcetide at a dose of 6.1 ± 3.1 mg/session at the end of the study. Among these 45 patients with iPTH levels of 60–240 pg/mg, 18/22 patients in the 25 mg cinacalcet group received ≤ 5 mg/session etelcalcetide and required no increase in dose. In the 50 mg cinacalcet group, a dose of

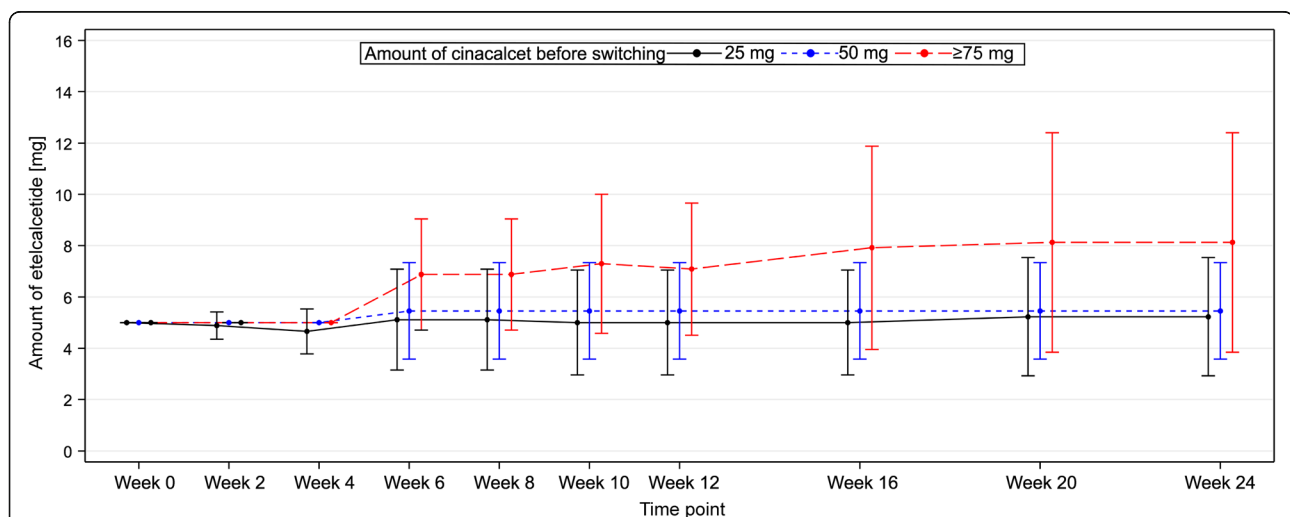


Fig. 5 Changes in the dose of etelcalcetide during the study in each dose group. The doses were 25, 50, and ≥ 75 mg ($n = 45$). For patients with intact PTH levels within the management target at screening and at the end of the study, the same doses of vitamin D agent and calcium-based phosphate binder were selected

Table 4 Distribution of etelcalcetide hydrochloride at the end of the study

Dose of cinacalcet before switching	Dose of etelcalcetide at week 24 after switching							Total
	0 mg	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	
25 mg	0	5	13	1	3	0	0	22
50 mg	0	1	8	1	1	0	0	11
≥ 75 mg	0	0	6	3	0	0	3	12
Total	0	6	27	5	4	0	3	45

5 mg/session was maintained in 8/11 (72.7%) patients. None of the patients in the ≥ 75 mg cinacalcet group required a dose reduction and 50% required a dose elevation.

The mean etelcalcetide dose used at the end of the study per group was 5.2 ± 2.3 mg/session (25 mg cinacalcet group), 5.5 ± 1.9 mg/session (50 mg cinacalcet group), and 8.1 ± 4.3 mg/session (≥ 75 mg cinacalcet group). Consequently, for patients taking 50 mg cinacalcet, the initial etelcalcetide dose of 5 mg/session was optimal during conversion. However, in the ≥ 75 mg cinacalcet group, the initial etelcalcetide dose was insufficient in 50% of the patients, and a dose elevation was recommended. In the 25 mg group, only a few patients required a dose elevation, and most patients received less than 5 mg/session, suggesting the need for a lower initial dose. According to Xipell et al. [19], the calculated dose of etelcalcetide used in the 25 mg cinacalcet group was 3.74 mg/session, lower than that in the present study. This may be due to the variability in the initial dose of etelcalcetide used by Xipell et al., as it was based on the prior dose of cinacalcet. However, in this study, the initial dose of etelcalcetide was 5 mg/session, as recommended in the package insert. Xipell et al. started etelcalcetide at a dose of 2.5 mg/session in the 30 mg

cinacalcet group. In the 25 mg cinacalcet group, reducing the dose to 2.5 mg/session may also be effective.

In this study, the ratio of etelcalcetide per session to oral cinacalcet per day increased with the increase in the spKt/V. Etelcalcetide was primarily cleared by HD, with approximately 60% of the administered dose eliminated in dialysate. Minor amounts were excreted in urine and feces [20]. Most patients enrolled in our study did not have urine output; it is likely that the excretion of etelcalcetide is mostly through hemodialysis. Therefore, among patients with high hemodialysis efficiency, the required amount of etelcalcetide may have increased due to the increased excretion of etelcalcetide. When switching from cinacalcet to etelcalcetide, hemodialysis efficiency should be considered in dose adjustment. The fact that there was no significant result among the 45 patients was likely due to the small number of patients.

The findings of this study suggest that switching to etelcalcetide when the iPTH level is > 240 pg/mL can help maintain the iPTH level within the reference range. Particularly, in the poorly controlled group (iPTH > 240 pg/mL), 17/22 (77.3 %) patients achieved the reference iPTH level, suggesting that etelcalcetide effectively decreases the iPTH level. It has been reported that etelcalcetide can decrease the iPTH level better than cinacalcet

Table 5 List of SHPT medication changes before and after the study

SHPT-related agent	Time	Dose of cinacalcet hydrochloride before switching			Total
		25 mg	50 mg	≥ 75 mg	
Active vitamin D agent	SCR	48 (90.6)	18 (100.0)	17 (89.5)	83 (92.2)
	24 weeks	50 (94.3)	17 (94.4)	18 (94.7)	85 (94.4)
Ca-based phosphate binder	SCR	30 (56.6)	9 (50.0)	7 (36.8)	46 (51.1)
	24 weeks	33 (62.3)	9 (50.0)	6 (31.6)	48 (53.3)
Lanthanum carbonate	SCR	37 (69.8)	14 (77.8)	15 (78.9)	66 (73.3)
	24 Weeks	34 (64.2)	14 (77.8)	13 (68.4)	61 (67.8)
Sevelamer	SCR	14 (26.4)	8 (44.4)	7 (36.8)	29 (32.2)
	24 weeks	12 (22.6)	7 (38.9)	7 (36.8)	26 (28.9)
Iron-based phosphate binder	SCR	14 (26.4)	2 (11.1)	7 (36.8)	23 (25.6)
	24 weeks	12 (22.6)	2 (11.1)	6 (31.6)	20 (22.2)
Bivalomer	SCR	6 (11.3)	1 (5.6)	1 (5.3)	8 (8.9)
	24 weeks	5 (9.4)	1 (5.6)	1 (5.3)	7 (7.8)

SHPT secondary hyperparathyroidism, SCR screening

Table 6 Adverse effects

Adverse effects	Severity					
	Mild		Moderate		Severe	
	Number	Number of patients (%)	Number	Number of patients (%)	Number	Number of patients (%)
All	3	2 (2.2)	0	0 (0.0)	0	0 (0.0)
Myocardial injury	1	1 (1.1)	0	0 (0.0)	0	0 (0.0)
Angina	1	1 (1.1)	0	0 (0.0)	0	0 (0.0)
General/systemic disorder and administration-site conditions	1	1 (1.1)	0	0 (0.0)	0	0 (0.0)
Discomfort	1	1 (1.1)	0	0 (0.0)	0	0 (0.0)
Infection and parasitic disease	1	1 (1.1)	0	0 (0.0)	0	0 (0.0)
Skin infection	1	1 (1.1)	0	0 (0.0)	0	0 (0.0)

and that it is more effective in patients with the above-management target iPTH level taking a high dose of cinacalcet [16]. In some poorly controlled cases, owing to gastrointestinal symptoms caused by cinacalcet, oral medication adherence is a problem. Therefore, switching to intravenously administered agents such as etelcalcetide may be useful in patients with poorly controlled SHPT.

The overall safety and tolerability of etelcalcetide and cinacalcet are similar [16]. In the present study, no significant differences in gastrointestinal AEs including vomiting and nausea were observed. The study comprised patients who safely received cinacalcet, which may have resulted in only a few new gastrointestinal AEs. Hypocalcemia is known to be caused by etelcalcetide. Here, the cCa levels decreased below 8.4 mg/dL in over 50% of the patients leading to etelcalcetide dose reduction and active vitamin D and CPBP dose adjustment. In seven patients, the cCa level decreased below 7.5 mg/dL during the study, the level at which etelcalcetide treatment would normally be ceased. As hypocalcemia was not an observed symptom, etelcalcetide dose reduction and active vitamin D and CPBP dose elevation were left to the discretion of the prescribing physician, and drug withdrawal was avoided. Therefore, hypocalcemia should be considered when replacing cinacalcet. After switching from cinacalcet 25 mg, 33/53 patients showed a cCa level of < 8.4 mg/dL. Furthermore, the cCa level significantly decreased in 45 patients with the reference iPTH level, and the requirement for active vitamin D and CPBP treatment suggested that etelcalcetide decreases the Ca level more than cinacalcet. Consequently, the Ca level should be closely monitored when switching to etelcalcetide.

The present study had some limitations: not placebo-controlled, had a small number of patients, possible presence of attrition bias, and included only Japanese patients, which may affect the generalizability of the results. In addition, the disease activity of SHPT can be altered during the 24-week study period. Therefore, the

prescribed doses at different time points might not be directly compared. This drawback can be solved by conducting a two-arm comparative or a cross-over trial. Therefore, further studies are needed.

Conclusions

We determined the conversion dose as well as the safety and efficacy of switching from cinacalcet to etelcalcetide in HD patients with SHPT. Our findings provide a basis for understanding the effects and implications of switching from cinacalcet to etelcalcetide.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s41100-020-00310-y>.

Additional file 1: Supplementary Table S1

Abbreviations

AE: Adverse event; BAP: Bone alkaline phosphatase; Ca: Calcium; cCa: Corrected calcium; CBPB: Calcium-based phosphate binder; CKD-MBD: Chronic kidney disease-mineral and bone disorder; FGF-23: Fibroblast growth factor 23; HD: Hemodialysis; iPTH: Intact PTH; K/DOQI: Kidney Disease Outcomes Quality Initiative; P: Phosphorus; SHPT: Secondary hyperparathyroidism; TRACP-5b: Tartrate-resistant acid phosphatase

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Authors' contributions

Y. Kurokawa, Y. Kaida, and KF prepared the manuscript. Y. Kurokawa, Y. Kaida, TH, YN, TO, RS, SI, GK, NN, TK, TM, AN, RA, YW, MS, MU, MC, AM, AO, and HM collected the clinical data. TK conducted the statistical analyses. All authors agreed to be accountable for all aspects of the work and to ensure that questions related to the accuracy of any part of the work are appropriately resolved. The authors read and approved the final manuscript.

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Availability of data and materials

Please contact the corresponding author for data requests. If the request is valid, we will share our data.

Ethics approval and consent to participate

This multicenter open-labeled study was conducted in conformity with the International Council for Harmonization (ICH)—Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the institutional review boards of Kurume University School of Medicine (No: 17001), Yame General Hospital (No: 17-001), Moriyama Clinic of Internal Medicine, Nagata Hospital, Sugi Cardiovascular Hospital, Yamaguchi Saiseikai General Hospital, Wada Cardiovascular Clinic, Usui Clinic, Chiba Naika Jyunkankika, and Miyazakinaika Medical Clinic: Clinical Research Network Fukuoka (No: 17-E06). This study has been registered in the University Hospital Medical Information Network clinical trials database (UMIN 000027637).

Consent for publication

Written informed consent was obtained from all patients before enrollment.

Competing interests

KF, Y. Kaida, and YN received consultant fees from Ono Pharmaceutical Co., Ltd. and Kyowa Hakko Kirin. Y. Kurokawa received consultant fees from Ono Pharmaceutical Co., Ltd. RS, SI, and TM received consultant fees from Kyowa Hakko Kirin. The others authors declare that they have no competing interests.

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