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Rationale and study design of a randomized controlled trial for development of a treatment strategy for chronic kidney disease–mineral and bone disorder by multilateral mechanism of etelcalcetide hydrochloride (the DUET study)

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Abstract

Background: Secondary hyperparathyroidism (SHPT) is a common complication in advanced chronic kidney disease (CKD). The aims of this study are to clarify the efficacy of etelcalcetide, a novel-approved intravenous calcimimetic, for evaluating the optimal therapy for etelcalcetide-induced hypocalcemia, and to identify sensitive markers for vascular calcification in patients undergoing maintenance dialysis.

Methods: The *D*evelopment of treatment strategy for CKD-MBD by m*U*ltilateral mechanism of *ET*elcalcetide hydrochloride (DUET) study is a 12-week multicenter, open-label, randomized (1:1:1), parallel-group study in SHPT patients undergoing maintenance hemodialysis. A total of 120 patients will be randomly assigned to etelcalcetide + active vitamin D, etelcalcetide + oral calcium preparation, or control (standard therapy) groups. If hypocalcemia is induced by etelcalcetide, active vitamin D and oral calcium preparations will be administered, in addition to the original medications, to patients allocated to etelcalcetide + active vitamin D and etelcalcetide + oral calcium preparation, respectively. The primary endpoint will be to compare the proportion of patients with a 50% reduction in serum intact parathyroid hormone (iPTH) levels after 12 treatment weeks with etelcalcetide relative to baseline values and iPTH levels ≤ 240 pg/mL at the 12-week time point after the trial starts between the intervention group and non-intervention group.

Results: The background, rationale, and study design of this trial will be also presented. To date, over 100 patients have been enrolled in this trial. The entire study will end in 2020.

Conclusion: The DUET trial will provide new evidence regarding the development of a treatment strategy using etelcalcetide for suitable control of iPTH levels and will define the optimal therapy for etelcalcetide-induced hypocalcemia in dialysis patients with SHPT.

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Keywords: Calciprotein particles, Clinical trial, Etelcalcetide, Hemodialysis, Secondary hyperparathyroidism

Background

The kidney plays a crucial role in the regulating minerals in the body including calcium and phosphorus [1]. Almost all patients with advanced chronic kidney disease (CKD) just before initiation of dialysis exhibit secondary hyperparathyroidism (SHPT) and hyperphosphatemia, i.e., chronic kidney disease–mineral and bone disorder (CKD-MBD). Treatments for SHPT include diet and medications such as active vitamin D (VitD) analogs, calcimimetics, phosphate binders, and a combination of these drugs [2]. If these treatments do not bring parathyroid hormone levels under control, parathyroidectomy is considered [2]. Currently, orally active VitD has been widely used as a supplement for treatment of SHPT in advanced CKD patients due to a lack of adequate endogenous active VitD. However, treatment with elevated doses of active VitD analogs for controlling intact parathyroid hormone (iPTH) is highly likely to induce hypercalcemia and hyperphosphatemia in maintenance dialysis patients. The calcium-sensing receptor (CaSR) plays an essential role in maintaining calcium homeostasis in the body. The parathyroid gland can sense slight changes in extracellular ionized calcium levels through the CaSR located on the parathyroid cell membrane and can quickly modify PTH secretion. Cinacalcet, a pharmacological calcimimetic agent, mimics the activity of calcium by allosteric activation of the CaSR. It was the first drug approved for clinical use in the USA in 2004 and in Japan in 2008 for the treatment of SHPT [3]. Cinacalcet has been demonstrated to effectively suppress iPTH levels in various clinical trials but has produced not few gastrointestinal adverse events [4].

Etelcalcetide is a second-generation calcimimetic agent approved for treatment of SHPT in 2017 in Japan concurrently with the USA and the European Union. Unlike cinacalcet, etelcalcetide is administrated intravenously at the end of each hemodialysis session, which may also result in improved adherence to calcimimetic therapy [4]. Etelcalcetide has a longer elimination half-life than cinacalcet, and its plasma concentration remains stable from 24 h post-dose to the next dialysis session [5]. In phase 1 and 2 clinical trials in Japan, etelcalcetide reduced serum iPTH levels in a dose-dependent manner while reducing serum calcium levels [6]. Moreover, in phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study, thrice-weekly administration of etelcalcetide for 12 weeks significantly reduced serum iPTH levels compared to placebo [7]. However, as hypocalcemia was more frequent following etelcalcetide treatment than with cinacalcet, the safety of etelcalcetide should be verified in a practical setting together with its effectiveness.

It is well known that hyperphosphatemia is associated with poor clinical outcomes and that phosphate restriction improves outcomes in CKD patients [2]. However, the molecular mechanism involved in cytotoxicity by phosphate overload remains unclear. Recent studies have suggested that the true culprit of phosphate toxicity is not phosphate per se but calciprotein particles (CPPs), which are colloidal nanoparticles composed of calcium phosphate crystals and mineral-binding proteins such as fetuin-A [8]. Although the physiological function of CPPs is to transport dietary phosphate and calcium to the bone, there have been numerous reports indicating that serum CPP levels increase with CKD progression [9–11]; serum CPP levels have also been reported to correlate with vascular calcification and atherosclerosis [10].

The aim of the ongoing trial, Development of treatment strategy for CKD-MBD by mUltilateral mechanism of ETelcalcetide hydrochloride (DUET study), is to perform a multicenter randomized controlled study of Japanese maintenance dialysis patients with SHPT. The primary outcome is to verify whether administration of etelcalcetide for 12 weeks significantly increases the ratio of patients who can achieve target iPTH levels, consisting of more than a 50% reduction of iPTH level and below 240 pg/mL, compared to current conventional therapy. The trial will also explore an optimal approach to correct hypocalcemia with etelcalcetide treatment and investigate how to suppress CPP levels as well as other markers related to bone metabolism.

Methods

Trial design

The DUET trial is a multicenter, open-label, randomized (1:1:1), parallel-group study aiming to clarify the effects and safety of etelcalcetide on the control of SHPT, to define an optimal approach to hypocalcemia treatment induced by etelcalcetide, and to evaluate the impact of etelcalcetide on CKD-MBD. This trial was initially registered in the Japanese University Hospital Medical Information Network Clinical Trials Registry (UMIN 000030927) and then in the Japan Registry of Clinical Trials (jRCTs041180108). The study protocol was approved by the Nagoya University Graduate School of Medicine Ethics Committee (No. 2017-0481). All patients have provided written informed consent to participate in this study after they received information about the

purpose of this study as well as the potential risks and benefits.

Patients

We have been recruiting study subjects since May 2018. The inclusion and exclusion criteria are shown in Table 1.

Registration and randomization

Patients were enrolled via a web-based registration and follow-up system organized by Nagoya University Hospital's Center for Advanced Medicine and Clinical Research, Aichi, Japan. Once a primary doctor who is a registered member of this research project obtains a patient's consent, he or she has access to this study's registration system and can enter the required information at enrollment. The system automatically evaluates the eligibility of each patient and randomly assigns patients to three groups: group E+D, etelcalcetide and additional active VitD on top of the original medications if hypocalcemia is induced by etelcalcetide; group E+Ca, etelcalcetide and additional oral precipitated calcium carbonate on top of the original medications if hypocalcemia is induced by etelcalcetide; or group C, control (standard therapy using VitD and precipitated calcium carbonate).

The allocation ratio is 1:1:1 and a dynamic allocation strategy using a minimization method was used. The stratifying factors for randomization are iPTH (> 400 pg/mL or ≤ 400 pg/mL), corrected serum calcium (> 9 mg/dL or ≤ 9 mg/dL), serum phosphate (> 5 mg/dL or ≤ 5 mg/dL) within 2 weeks before the trial starts, and the institution to which the patients belong.

Table 1 Eligibility criteria

Inclusion criteria
1. Patients undergoing maintenance hemodialysis three times per week
2. Patients with dialysis vintage ≥ 1 year
3. Patients with stable disease judged from medical records, physical examination, and laboratory tests
4. Patients between 20 and 99 years of age
5. iPTH levels ≥ 240 pg/mL for 4 months prior to the enrollment
6. Corrected serum calcium level ≥ 8.4 mg/dL at enrollment
7. Provision of written informed consent
Exclusion criteria
1. A history of administration of etelcalcetide
2. Administered bisphosphonates within 24 weeks of providing informed consent
3. Primary hyperparathyroidism
4. A history of parathyroidectomy or underwent interventional treatment of the parathyroid gland within 90 days of providing informed consent
5. Scheduled to undergo parathyroidectomy or interventional treatment on the parathyroid gland
6. Pregnant, breast feeding, or desire to bear children
7. Severe complications including cancer causing hypercalcemia or severe infection at the time of providing informed consent
8. Administered either, maxacalcitol over 10 μg three times weekly, calcitriol over 0.75 μg three times weekly, calcitriol over 0.75 μg three times weekly, another active VitD above half of the maximum dose, or precipitated calcium carbonate over 3 g/day
9. Considered unsuitable to participate in this study as per the primary doctor's judgment

VitD vitamin D, *iPTH* intact parathyroid hormone

Procedures

Eligible participants were randomly assigned (1:1:1) to group E+D, group E+Ca, or the control group. An enrolled patient who was not treated with oral calcimimetics including either cinacalcet or evocalcet started intervention 2 weeks after allocation. For patients treated with oral calcimimetics, the intervention started after an 8-week washout period from calcimimetics. The intervention period was 12 weeks. The study drug (etelcalcetide) was injected into the venous line of the dialysis circuit after each dialysis session three times per week. The starting dose was 5 mg and was to be increased in 2.5 mg or 5 mg increments at 4 and 8 weeks based on the target iPTH level calculated to achieve the primary outcome. Etelcalcetide was temporarily withheld for severe low-corrected serum calcium level (< 7.5 mg/dL) and considered for re-administration after recovery from hypocalcemia (corrected serum calcium ≥ 8.4 mg/dL). When re-administering etelcalcetide, it was allowed to reduce the dose. The dose of etelcalcetide was set at between 2.5 mg and 15 mg. iPTH, serum correct calcium, and serum phosphate levels were monitored every 2 weeks. If a patient in group E+D or in group E+Ca showed mild to low-corrected serum calcium levels (< 8.4 mg/dL), we attempted to amend hypocalcemia with active VitD and oral calcium carbonate, respectively. If a patient was in group C, we controlled SHPT without any calcimimetics. Any drug with a potential interaction with the control of SHPT, such as bisphosphonates and denosumab, was prohibited throughout the study period. We also restricted a change in type or dose of prior VitD treatment in the E+Ca group and of calcium carbonate in the E+D group, respectively. The study flowchart is shown in Fig. 1.

Biochemical data and other determinants

Biochemical data was collected prior to hemodialysis at baseline and periodically throughout the 12-week interventional term as follows: measurement of calcium, phosphate, albumin, and iPTH levels every 2 weeks; total protein, creatinine, blood urea nitrogen, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GTP), and alkaline phosphatase (ALP) every 4 weeks; high-sensitivity C-

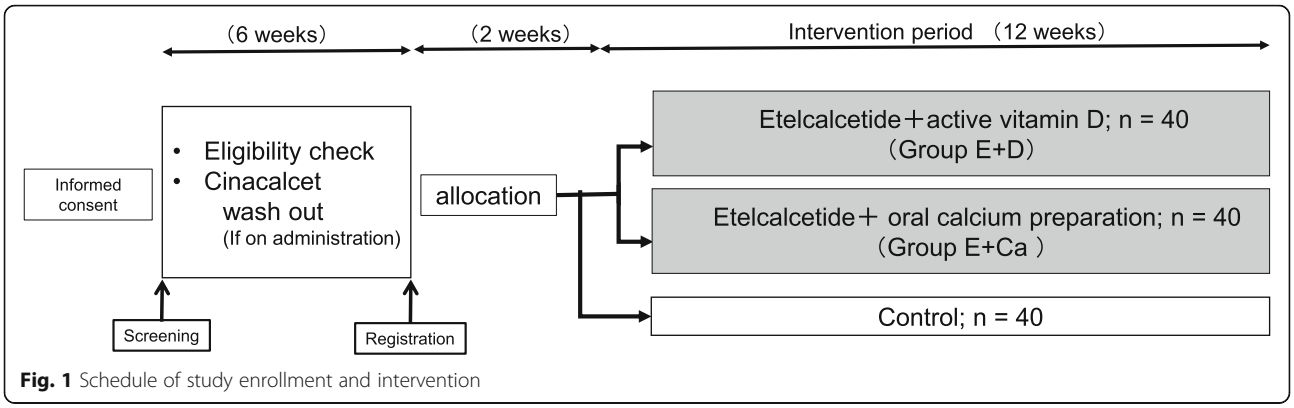

Fig. 1 Schedule of study enrollment and intervention

reactive protein (hsCRP) and interleukin 6 (IL-6) every 6 weeks; bone-specific ALP (BAP) and tartrate-resistant acid phosphatase 5b (TRACP-5b) at baseline and 1 year after the start of trial; and complement component 3 (C3), complement component 4 (C4), CH50, 1,25-(OH)2 VitD, and 25-(OH) VitD at baseline, and was entrusted to the laboratory of BML Inc., Aichi, Japan. Measurement of fibroblast growth factor 23 (FGF23) and CPP was arranged every 6 weeks at the laboratory of SRL Inc., Aichi, Japan, and at the Division of Anti-Aging Medicine, Center for Molecular Medicine, Jichi Medical University, Tochigi, Japan, respectively. The method used for CPP determination will be performed by the method as described previously [12].

Endpoints

The primary endpoint of the protocol is the proportion of achievement of more than a 50% reduction and iPTH levels to under 240 pg/mL after 12 weeks of treatment. The secondary endpoints are the proportion of achievement after 12 weeks of treatment (1) to iPTH 60 ≤ iPTH ≤ 240 pg/mL, (2) achievement of more than 50% reduction in iPTH levels, (3) achievement of more than 30% reduction in iPTH levels, and (4) achievement of more than 30% reduction and iPTH levels 60 ≤ iPTH ≤ 240 pg/mL. Between the group treated with etelcalcetide and the control group, and among the three treatment groups, (5) changes in iPTH levels after 2, 4, 6, 8, 10, and 12 weeks of treatment relative to the baseline, (6) changes in CPP and FGF23 levels after 6 and 12 weeks of treatment relative to baseline values, (7) changes in calcium, phosphate, calcium-phosphate product, and magnesium levels after 2, 4, 6, 8, 10, and 12 weeks relative to the baseline values, (8) changes in BAP and TRACP-5b levels after 1 year of treatment relative to baseline values, and (9) comparison of aortic calcification before and after observation will also be investigated as secondary outcomes. In addition, we plan to (10) compare the normalized ratio of hypocalcemia induced by etelcalcetide between group E+D and group E+Ca.

Moreover, the rate of adverse drug reactions will be checked for safety.

Follow-up

We will follow-up patients for 12 weeks after study commencement and data concerning adverse events, drug adherence, physical examination, blood pressure, and laboratory tests as described above will be obtained. A precautionary decision will be made to discontinue the study for any patient whose corrected serum calcium level falls under 6.5 mg/dL, defined as uncontrolled hypercalcemia.

Sample size

Based on the results of a previous clinical trial [7] and taking into account a registered patient background, we assumed that 35% of patients in the intervention group will achieve a lower than iPTH normalization rate (iPTH 240 pg/mL). After assuming a 10% normalization rate in the control group, we calculated that at least 76 individuals were necessary in the intervention group to detect a significant difference with a power of 0.85 and significance level of 0.05. We speculated that the normalization rate would be higher than that of the previous report and set the number of intervention patients to 80, with 40 control patients, and thus, a total of 120 patients were foreseen in total.

Statistical analysis

The validity/safety will be analyzed in the largest analysis target group (full analysis set; FAS) defined below. For the definition of the FAS, subjects shall satisfy all the following criteria: (1) patients who meet the selection criteria and do not satisfy the exclusion criteria, (2) patients who measured at least one marker to evaluate efficacy after administration (regardless of the primary or secondary endpoint). The analysis method for the primary outcome will be as follows: (1) calculate the achievement proportion of iPTH 50% reduction and iPTH ≤ 240 pg/mL at 12 weeks after administration, and 95% confidence intervals (CI) based on binomial distribution for each treatment

group; (2) compare the achievement proportion calculated between the groups treated with etelcalcetide (group E+D and group E+Ca) and the control group (group C) by logistic regression analysis with PTH, Ca, and P as covariates, and in addition (3) when a statistical significant difference was obtained, compare the achievement proportion between group E+D and group E+Ca. A P value < 0.05 was considered statistically significant.

The analysis methods for the secondary outcomes are shown in Table 2.

Results

The target number of patients to be enrolled is 120 (1:1:1 = group E+D: group E+Ca: control). The Nagoya University Graduate School of Medicine Ethics Committee approved this protocol on March 13, 2018. We enrolled the first patient on May 7, 2018. By the end of December of 2018, the study had enrolled 114 patients from 13 participating dialysis centers and is currently recruiting patients. This study will end in 2020.

Discussion

Chronic kidney disease (CKD) is kidney damage that occurs slowly over many years and the prevalence of changes in calcium and phosphorus levels increases as the estimated glomerular filtration rate (eGFR) declines and finally constitutes SHPT. Various studies have suggested that SHPT may be associated with mortality in itself [13–15]. Moreover, CKD-MBD is deeply associated with vascular calcification and in turn leads to high cardiovascular mortality as well as dysfunction of bone metabolism [16].

Since the recent arrival of calcimimetics, the management of SHPT in maintenance hemodialysis patients has reached a major turning point [17, 18]. There were randomized clinical trials (RCTs) which reported that cinacalcet could ameliorate vascular calcification and, in turn, reduce the high cardiovascular mortality [19–21]. However, persuasive evidence of the effects of cinacalcet on hard outcomes remains elusive [22]. Although cinacalcet does not yet have confirmed evidence in hard outcomes, we believe that calcimimetics have the potential to reduce vascular calcification and in turn the high cardiovascular mortality.

There have been few reports evaluating the practical use of etelcalcetide in the control of SHPT as well as CKD-MBD and mortality. In a phase 3 RCT involving 1023 hemodialysis patients with moderate-to-severe SHPT, patients randomized to etelcalcetide significantly achieved a targeted iPTH level compared to patients on placebo [23]. In this study, the authors also showed that FGF 23 levels in patients with etelcalcetide were lower than those in patients on placebo despite the more frequent provision of calcium and VitD. In the RCT using etelcalcetide and cinacalcet involving 683 hemodialysis patients with SHPT, etelcalcetide was not inferior to cinacalcet in the control of iPTH levels over 26 weeks [24]. Therefore, in this DUET study, we will demonstrate that etelcalcetide improves the management of SHPT safely in Japanese maintenance hemodialysis patients; furthermore, the study will evaluate whether etelcalcetide suppresses CPP, a marker of vascular calcification.

Table 2 The analysis methods for the secondary outcomes

Secondary outcomes	The analysis method for the secondary outcomes
1) The proportion of achievement of 60 ≤ iPTH ≤ 240 pg/dL after 12 weeks of treatment 2) The proportion of achievement of more than a 50% reduction in iPTH levels after 12 weeks of treatment 3) The proportion of achievement of more than a 30% reduction in iPTH levels after 12 weeks of treatment 4) The proportion of achievement of more than a 30% reduction and 60 ≤ iPTH ≤ 240 pg/dL after 12 weeks of treatment	• Calculate the achievement proportions of the targets 1 to 4 at 12 weeks after administration, and 95% confidence intervals (CI) based on the binomial distribution for each treatment group. • Compare these achievement proportions between the groups treated with etelcalcetide (group E+D and group E+Ca) and the control group (group C) by logistic regression analysis with iPTH, Ca, and P as covariates. • When a statistical significant difference is obtained, compare the achievement proportion between group E+D and group E+Ca by logistic regression analysis.
5) Changes in iPTH levels after 2, 4, 6, 8, 10, and 12 weeks of treatment relative to the baseline 6) Changes in CPP and FGF23 levels after 6 and 12 weeks of treatment relative to the baseline 7) Changes in calcium, phosphate, calcium-phosphate product, and magnesium levels after 2, 4, 6, 8, 10, and 12 weeks relative to the baseline 8) Changes in BAP and TRACP-5b levels after 1 year of treatment relative to baseline 9) Changes in aortic calcification before and after observation	• Calculate the adjusted mean and the 95% CI for changes at each time point by a linear mixed model with each treatment group, time point, and interaction of the treatment group and time point as the fixed effects. • Compare between treatment groups using a linear mixed model with values of each index at baseline, treatment groups, time points, interaction between treatment groups and time points as the fixed effects and changes of each index as response variables. • Compare changes of each index among treatment groups at each time point using the Tukey-Kramer method to correct for multiplicity.
10) Normalized proportion of hypocalcemia induced by etelcalcetide between group E+D with group E+Ca	• When hypocalcemia occurs in the group E+D and group E+Ca, calculate the normalized proportions with 95% confidence intervals (CI) based on binomial distribution for each treatment group. • Compare normalized proportions between group E+D and group E+Ca using logistic regression analysis with iPTH, Ca, and P as covariates.

Because calcimimetics increase the sensitivity of the calcium-sensing receptor (CaSR), the use of calcimimetics induces a decrease in PTH secretion and suppresses serum Ca, which potentially results in hypocalcemia. In the abovementioned RCT using etelcalcetide, 77.9% of the patients developed hypocalcemia [23], 47.0% showed mild hypocalcemia, and 7.9% presented symptomatic hypocalcemia in the recent trial evaluating the safety of etelcalcetide for 1 year [25]. Although integrated analysis of the safety profile of eletcalcetide described that the majority of cases of hypocalcemia related to eletcalcetide were mild to moderate in severity, and serious cases were infrequent [26], drugs for normalization will be needed. Indeed, the proportion of patients using active VitD and calcium-containing phosphate binders for normalization of hypocalcemia increased over time [23, 25]. In this way, an excess calcium load may accelerate vascular calcification. We also believe that we can obtain information for better correction of hypocalcemia from the comparison of vascular calcification markers between group E+D and group E+Ca in this trial.

In conclusion, the DUET study is the first randomized controlled study on etelcalcetide to assess its efficacy of iPTH-controlling ability with a concurrent assessment of the best way to correct hypocalcemia. In addition, changes in the surrogate markers of vascular calcification, especially CPP, will aid in selecting a treatment for its prevention. Although further studies are needed, this trial will provide evidence for the optimal therapy for SHPT in maintenance hemodialysis patients and will contribute to improving the control of CKD-MBD.

Abbreviations

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BAP: Bone-specific ALP; C3: Complement component 3; C4: Complement component 4; CACS: Agaston coronary artery calcification scores; CaSR: Calcium-sensing receptor; CKD: Chronic kidney disease; CKD-MBD: Chronic kidney disease–mineral and bone disorder; CPPs: Calciprotein particles; CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; FAS: Full analysis set; FGF23: Fibroblast growth factor 23; hsCRP: High-sensitivity C-reactive protein; IL-6: Interleukin 6; iPTH: Intact parathyroid hormone; RCT: Randomized clinical trial; SHPT: Secondary hyperparathyroidism; TRACP-5b: Tartrate-resistant acid phosphatase 5b; VitD: Vitamin D; γ-GTP: γ-Glutamyl transpeptidase

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Authors' contributions

SK and MT were responsible for the research idea, study concept, and design and had the primary responsibility of studying and writing the paper. YI took part in composing the study protocol and constructed the study management team. MA constructed the statistical analysis plan and data management system. SM was also responsible for the research idea, the study concept, and designing and organizing the study as a principal investigator, as well as supervising the writing of the paper. All authors read and approved the final manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval and consent to participate

The study was performed according to Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labor and Welfare; the laws and regulatory requirements of Japan; and the ethical principles stated in the Declaration of Helsinki. The protocol, amendments, and subject informed consent forms were approved by the Nagoya University Graduate School of Medicine Ethics Committee (No. 2017-0481).

Consent for publication

All co-authors approved this submission. The patients consented to publish their information details.

Competing interests

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