




## STUDY PROTOCOL

# REVISÉD Protocol for a randomized study of the efficacy of ibandronic acid plus eldecacitol in patients with gastric cancer after gastrectomy: A comparative study of different routes of administration of ibandronic acid [version 2; peer review: 2 approved]

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## Abstract

**Background:** Patients who undergo gastrectomy for gastric cancer are susceptible to osteoporosis. To prevent a decrease in bone mineral density, an appropriate prophylaxis is considered important to adjust the post-gastrectomy condition. In this study, we will compare two different routes of administration of ibandronic acid (oral or intravenous) plus eldecacitol as a potentially more suitable treatment for patients at a high risk of fragile fracture.

**Protocol:** This study protocol describes a randomized, active-controlled, non-blind, single-center, phase II trial. For patients in the investigational arm (Group A), sodium ibandronate hydrate will be administered intravenously once a month with daily oral intake of eldecacitol; for those in the control arm (Group B), sodium ibandronate hydrate will be administered orally once a month with daily oral intake of eldecacitol. We will recruit patients aged 45–85 years who have undergone gastrectomy for gastric cancer and are at a risk of fragility fractures. The study will include patients with existing vertebral fractures and/or femoral proximal fractures, or with lumbar and/or proximal femur bone mineral density of less than 80% of the young adult mean. The primary outcome of this study will be the change in lumbar bone mineral density. We will also evaluate the

## Open Peer Review

Approval Status  

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- Carlen Reyes** , Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
- Friederike Thomasius**, Frankfurter Hormon Und Osteoporosezentrum, Frankfurt, Germany

Any reports and responses or comments on the

changes in femur bone mineral density, bone metabolism markers, health-related quality of life as evaluated using the EuroQol 5 Dimension (EQ-5D), and digestive symptoms as evaluated using the Gastrointestinal Symptom Rating Scale after 52 weeks of treatment.

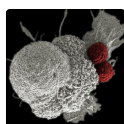
**Conclusions:** We believe that appropriate treatments that are adjusted to the condition of patients after gastrectomy are important for the prevention of bone mineral loss.

**Registration:** This study was accepted by the Japan Registry of Clinical Trials (jRCT1041200059, November 6, 2021).

### Keywords

osteoporosis, gastric cancer, post-gastrectomy, ibandronic acid, eldelcalcitol

article can be found at the end of the article.



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**REVISED Amendments from Version 1**

We have received comments and suggestions from two reviewers and have made revisions accordingly.

Reviewer 1 suggested narrowing the age range of participants and we changed to reflect this suggestion (45-85). Reviewer 1 also asked us to clarify the definition of patients at high risk of osteonecrosis of the jaw. Reviewer 1 recommended substitute the primary outcome from lumbar BMD for hip BMD since osteophytes and osteoarthritis in lumbar can interfere with bone densitometry measurements.

Reviewer 2 provided several comments regarding the study protocol. Reviewer 2 stated that we should add questions regarding calcium intake and supplements, and baseline calcium values in the screening periods. Also, they recommended us to add contraindications for Ibandronic acid therapy the inability to sit or stand in an upright position, stenosis of the esophagus or achalasia, and hypersensitivity to Ibandronic acid.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

Patients who have parts of their stomachs removed due to gastric cancer may suffer from low nutrition, impaired calcium absorption, and bone metabolism disorder, which have been reported as post-gastrectomy complications.<sup>1,2</sup> Although oncologic outcomes have improved in terms of long-term survival of patients with gastric cancer,<sup>3</sup> more attention should be paid to maintenance and improvement of quality of life (QOL) of patients. Currently, while more than 10 million people in Japan have osteoporosis and the prevalence of osteoporosis after gastrectomy is reportedly 40%,<sup>4-6</sup> awareness of how to reduce this post-operative risk remains insufficient. Moreover, it has been reported that osteoporosis is likely to occur due to malnutrition associated with nausea and ulceration of the mucosa as a result of anticancer drugs.<sup>7</sup> Thus, the prevention of a possible decrease in bone mineral density, and if necessary, the treatment of osteoporosis, is considered important to prevent future fragile fractures. Moreover, as multi-disciplinary liaison between enterogastric surgeons and physicians who treat osteoporosis does not always occur, some patients do not receive examinations for osteoporosis or appropriate treatments. Better awareness of the risks of osteoporosis is urgently needed for both patients and doctors.<sup>8</sup>

Administration of eldcalcitol, an active vitamin D preparation, is assumed to be effective in compensating for the poor intake of vitamin D after gastrectomy.<sup>9</sup> Furthermore, bisphosphonate is effective against osteoporosis, by inhibiting osteoclast function,<sup>10</sup> and its usefulness has been proven in post-gastrectomy gastric cancer.<sup>11</sup> However, the use of oral bisphosphonates (especially nitrogen-containing alendronate) may induce several adverse events.<sup>12</sup> On the contrary, ibandronic acid, a type of bisphosphonate, has binary administration routes—oral intake and intravenous infusion<sup>13</sup>—but it is not clear which route is suitable for patients with gastric cancer after gastrectomy. Therefore, we aim to examine the efficacy of eldcalcitol and ibandronic acid on bone metabolism in patients in the postoperative stage of gastric cancer, focusing on the usefulness of different ibandronic acid administration routes in this randomized, active-controlled, non-blind, single-center (academic hospital in Japan), phase II trial.

**Protocol****Overall study design**

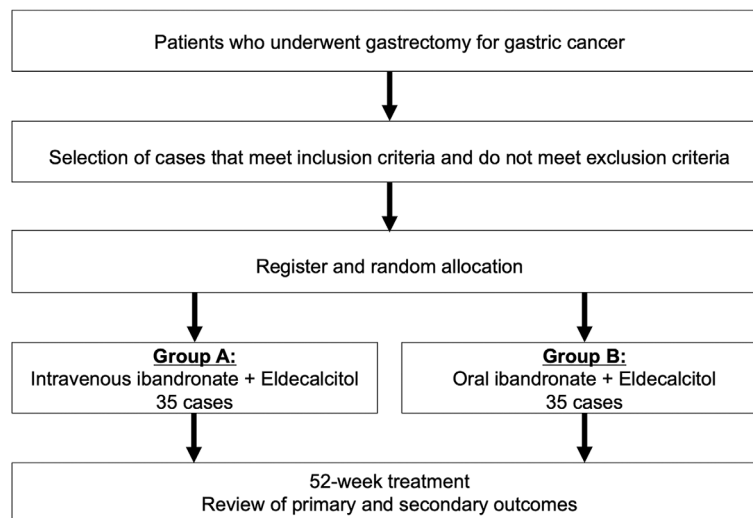
This study was approved by the Japan Registry of Clinical Trials (jRCT), approval number [jRCT1041200059](#), on November 6, 2021. The aim of this study is to evaluate the efficacy of different routes of ibandronic acid administration (oral tablets and intravenous injection) on bone mineral density, focusing on the digestive symptoms of patients after gastrectomy. The overall study flow chart is shown in [Figure 1](#). This study protocol follows the SPIRIT guidelines.<sup>30</sup>

We are conducting this trial in accordance with the principles of the Declaration of Helsinki. The Nagoya City University Certified Review Board (CRB4200003) approved this study (deliberation number 2020B003, November 6, 2021). Written informed consent will be obtained from all trial participants by physicians in charge. Physicians and medical institutions involved in this research will cooperate with the monitoring procedure manual and carry out this study in compliance with clinical research methods, related notices, and good clinical practice.

To ensure compliance with the protocol treatment, the attending physicians will ask patients about the medication status at each visit and offer guidance if there is any negligence of medication. The attending physicians will confirm the status of compliance with this study.

**Drugs**

For patients in the investigational arm (group A), sodium ibandronate hydrate (Bonviva<sup>®</sup> intravenous infusion 1 mg syringe; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) will be administered intravenously once a month with daily



**Figure 1. Flow chart of the study protocol.**

oral intake of eldecalcitol (Edirol<sup>®</sup> Capsule 0.75 µg; Chugai Pharmaceutical Co., Ltd.). For patients in the control arm (Group B), sodium ibandronate hydrate (Bonviva Tablets 100 mg; Chugai Pharmaceutical Co., Ltd.) will be administered orally once a month with a sufficient amount of water (approximately 180 mL) upon waking, with daily oral administration of eldecalcitol. For patients with hypercalcemia (corrected Ca = 10.5 mg/dL or more) identified at the time of registration or administration period, eldecalcitol dose will be reduced to appropriately 0.5 µg daily. Concomitant therapy will be permitted, including palliative and supportive therapies, such as analgesics, antiemetic agents, and anti-vomiting agents, for any symptoms due to primary disease or any adverse events. Additionally, chemotherapy for gastric cancer will be permitted. The usage of bone modulators and calcium/vitamin D supplements will not be permitted.

### Patients

We will recruit patients aged 45–85 years who underwent gastrectomy for gastric cancer and are at a risk of fragility fracture. The inclusion criteria will be as follows and all should be complied: i) patients who underwent total or partial gastrectomy for gastric cancer; ii) patients with existing vertebral fractures and/or femoral proximal fractures or with lumbar and/or proximal femur bone mineral density of less than 80% of the young adult mean (YAM); iii) patients with a relatively stable general condition (performance status [PS], 0–2); iv) patients aged ≥45 years and <85 years on the registration date; v) patients less than six months after gastrectomy; and vi) patients with their latest blood test (within 14 days before registration examination) complying with all of the following criteria: white blood cell count ≥ 1,500/µL; platelet count ≥ 100,000/µL; total bilirubin level ≤ 1.5 mg/dL; aspartate aminotransferase level ≤ 100 IU/L; alanine aminotransferase level ≤ 100 IU/L; serum creatinine level ≤ 1.5 mg/dL; and corrected Ca value < 10.5 mg/dL.

The exclusion criteria will be as follows and all should be complied: i) surgical resection extending to organs other than the stomach (*e.g.*, esophagus and pancreas); ii) patients with long-term immobility and inability to sit or stand in an upright position; iii) pregnant or breastfeeding women; iv) patients with a history or high risk of osteonecrosis of the jaw; v) patients with a history of hypocalcemia; vi) patients with urolithiasis; vii) patients with a history of allergy to the drugs used in this study; viii) patients with distant metastasis (including ascites cytology positive patients) at the time of registration; ix) patients with anorexia; x) patients who are being treated for osteoporosis at the time of registration; xi) stenosis of the esophagus or achalasia; xii) history of the hypersensitivity to ibandronate; xiii) patients who have socioeconomic problems or are assumed not to be supportive to this study. The risk of osteonecrosis will be assessed by the examination of dentists based on the presence of chronic periodontitis, necessity of exodontia or poorly-fitting denture.<sup>14</sup>

### Randomization

The patient registration center will randomly assign patients to one of two treatment groups. The target number of patients in each group is 35. A computer-generated random sequence, made by Clinical Research Management Center in Nagoya City University Hospital, will be used to allocate a total of 70 patients with no stratification to sequential identification. An independent allocation manager will be responsible for the allocation process, and the allocation list will be concealed an envelope until interventions are assigned.

## Target outcomes

The primary outcome of this study is the change in lumbar bone mineral density. Bone mineral density will be measured based on the dual-energy X-ray absorptiometry (DEXA) method. Bone mineral density will be evaluated during the pre-observational period, 24 weeks after the start of medication, and at the time of final observation (52 weeks after the start of medication). In addition, the following secondary assessments will be performed: i) change in femur bone mineral density (if patients with the presence of osteophytes and osteoarthritis on the X-ray of spine, femur bone mineral density will be substituted for lumbar bone mineral density); ii) change in bone metabolism markers, including serum cross-linked C-telopeptide of type I collagen (CTX), tartrate-resistant acid phosphatase 5b (TRACP-5b), total type 1 amino-terminal propeptide (P1NP), and 25OH vitamin D concentration (ELISA method); iii) change in health-related QOL, evaluated using the EuroQol 5 Dimension (EQ-5D)<sup>15</sup> at the start date of medication, 12 weeks after the start of medication, 24 weeks later, and at the time of final observation (after 52 weeks); iv) change in digestive symptoms, evaluated using the Gastrointestinal Symptom Rating Scale (GSRS)<sup>16</sup> at the start date of medication, 12 weeks after the start of medication, 24 weeks later, and at the time of final observation (after 52 weeks); v) presence or absence of fracture events during the medicated period; and vi) medication compliance rate. A total of 13 ibandronic acid doses will be scheduled in both groups over 52 weeks. The actual number of medications/13 will be calculated as the medication compliance rate.

## Schedule

In the pre-observation period, medical interviews will be conducted focusing on the patients' backgrounds including sex, age, height, weight, menopausal age, current medication, medical history (presence or absence of past fractures), eating habits, intake of vitamin D or Ca supplements, drinking/smoking history, presence or absence of femoral fractures in their parents, the area of extension of gastrectomy and the length of the remaining stomach, reconstruction techniques after gastrectomy, surgical intervention (open/laparoscopy/robot-guide), presence or absence of gallbladder resection, and presence or absence of post-operative anticancer drugs. In addition, the mineral density of the lumbar spine and femur will be measured using the DEXA method. Spine radiography will be performed in two directions: front and side in a standing position around the 4th lumbar vertebra and the 9th thoracic vertebra. The alignment of the entire spine and the existing fracture will also be confirmed. After confirming the selection criteria using medical charts and blood tests, the physicians will obtain written informed consent from all trial participants.

On day one of the trial, vital signs, blood test results, bone metabolism markers (CTX, TRACP-5b, P1NP, and 25OH vitamin D concentrations (using ELISA)), and physical function (EQ-5D and GSRS) will be examined.

After the start of medication administration, the following will be recorded: vital signs; medication status; the presence of adverse events; presence or absence of new fracture events; blood tests (to determine whether patients comply with the same criteria from the inclusion periods); bone metabolic markers; improvement in physical function evaluation (EQ-5D and GSRS); and bone density measurement (lumbar spine and femur). Subsequently, medical checks for vital signs, compliance with medication, and the presence of adverse events will be performed at 4, 12, 24, and 52 weeks. After the discontinuation of drug administration, observation and investigation will be conducted up to 4 weeks after the date of the last administration of the research drug. If adverse events continue, follow-up and investigation will be continued until recovery from the adverse events (Table 1).

## Safety

To evaluate safety, adverse events considered to be related to the research medicine will be monitored. Digestive symptoms, abnormality of calcium concentrations will be checked carefully on medical checks. Dubious symptoms for osteonecrosis of the jaw or atypical femoral fracture will be targeted to the further evaluations. All serious adverse events will be reported from the start of drug administration to the end of the follow-up period, along with the relationship among the type, severity, treatment content, time of expression, and turning point. Adverse events will include all undesirable or unintended symptoms and signs (including abnormalities in laboratory tests). The adverse events will be grade based on the Common Terminology Criteria for Adverse Events version 5. Serious adverse event is defined as an adverse event that is fatal, life threatening, requires in-patient hospitalization or prolonged hospitalization, results in persistent or significant disability/incapacity or other significant medical hazards. Follow-up investigations will be performed until the disappearance of/or recovery from adverse events. All serious adverse events will be reported to the Certified Review Board by the physicians in charge. The investigators shall promptly and appropriately treat the subjects and record the adverse event, date of onset, severity, and outcome, as well as ascertain the causal relationship of the study drug.

## Data collection methods

The data will be collected using a unified Case Report Form, which can be found as *Extended data*<sup>29</sup> and dissemination of the GSRS and EQ-5D charts.

**Table 1. Assessment and evaluation schedule.**

Stages of the study	Screening and exam description	Registration	0 weeks	4 weeks	12 weeks	24 weeks	52 weeks	4 weeks after discontinuation or cessation of drug administration	
Informed consent	○								
Allocation to Group A and Group B	○	○							
Patient background <sup>a</sup>	○								
Vital signs	○		○	●	●	●	●	●	
Bone density measurement (lumbar spine, proximal femur)	○					●	●		
X-ray of the spine	○						●		
Blood test <sup>b</sup>	○		○		●	●	●		
Bone metabolism markers			○		●	●	●		
Administration of research drugs <sup>*</sup>					↔				
Checking the proper medication				●	●	●	●		
EQ-5D, GSRs			○		●	●	●		
Checking adverse events <sup>c</sup>				↔					

Abbreviations: EQ-5D, EuroQol 5 Dimension; GSRs, Gastrointestinal Symptom Rating Scale.

○: Items to be recorded before the start of administration of the research and control drugs.

●: Items to be recorded after the start of administration of the research and control drugs.

<sup>a</sup>Collection of information on drugs related to the efficacy or safety of the research drug.

<sup>b</sup>Hematological testing of white blood cell count, red blood cell count, hemoglobin, hematocrit, and platelet count. Testing of alkaline phosphatase, aspartate aminotransferase (glutamate oxalacetate transaminase), alanine aminotransferase (glutamic pyruvic transaminase), lactate dehydrogenase,  $\gamma$ -glutamyl transpeptidase, creatine kinase, total bilirubin, total protein, albumin, urea nitrogen, creatinine, amylase, sodium, potassium, creatinine, calcium, and inorganic phosphorus levels, and estimated glomerular filtration rate to confirm the safety of the study.

<sup>c</sup>Adverse events are all unfavorable events regardless of a causal relationship with drugs.

<sup>\*</sup>Delays in the administration of test and control drugs will be acceptable for up to two weeks. If delayed, the observation date will be changed according to the number of days.

### Data management

All individuals involved in this research will properly handle the information of the research subjects and protect the personal information according to the “Act on the Protection of Personal Information.” The information of all patients involved in this study will be confidentially handled using the research specific identification code. Only the principal investigator (H.A.) will handle correspondence table between autonyms and anonyms. During the research, related information will be managed using a highly secured offline computer. Quality of the data will be checked during the data monitoring process.

### Statistical analysis

Statistical analysis will be performed within six months after data collection and enrollment of the final research participant. As it is predicted that the number of events will not be sufficient to make an early cancellation decision in the middle of registration, an intermediate analysis will not be performed.

The effectiveness of the investigational drugs will be evaluated using the intent-to-treat analysis for all eligible patients. The full analysis set (FAS) will comprise the entire group excluding the following research subjects: patients who do not meet the inclusion criteria, those who meet the exclusion criteria, those who are never administered drugs, and those for whom data are not obtained after the start of research medication. In the FAS, the per-protocol set (PPS) will comprise the entire group excluding the following research subjects: those for whom data on the main evaluation items are not obtained 52 weeks after the start of medication or those with a medication compliance rate of less than 80%. The sample size calculation was based on a previous study,<sup>3</sup> which reported that another bisphosphonate preparation (alendronate internal use) and eldecacitol increased lumbar bone density by approximately 6% at 12 months after administration compared with an increase of approximately 3% with eldecacitol alone. We expect the difference between the intravenous infusion and oral intake combined with eldecacitol will show 1.5% higher lumbar bone mineral density at 52 weeks (set to half of the additional effect of alendronate in the above previous study). The number of patients required to detect this with statistical significance is estimated to be 29 in each group with standard deviation 2%, significance level 5% (bilateral sides), and power 80%. Therefore, the target number of patients in this study is 35 (70 patients in total) in each group with the expectation that several patients will drop out.

To analyze effectiveness in the FAS and PPS, the rate of change in the bone mineral density from before the start of treatment will be calculated with respect to the lumbar bone mineral density at 52 weeks, and a comparison between groups will be performed using a Student’s *t*-test. In addition, for the analyses of secondary evaluation items in the FAS and PPS, the rate of change from before the start of treatment will be calculated for bone metabolism markers (TRAPC5b, PINP), femoral bone mineral density, and QOL (EQ-5D, GSRs) at 52 weeks using a Student’s *t*-test for comparison between groups. The frequency of fragile fracture events in each drug group will be calculated, and an intergroup comparison will be performed using a chi-square test.

Only the principal investigator (H.A.) will prepare a correspondence table of the research subject identification code set and only the principal investigator and biostatistician (H.H.) can access the final trial dataset.

### Data monitoring

In this clinical study, an independent data monitoring officer (Y.G.) will be assigned. On-site monitoring will be conducted to confirm whether the study is carried out safely and according to the research plan and whether the data are collected reliably. Monitoring will be conducted before the start of the research, during the research (every three months), and at the end of the research. In addition, monitoring will be carried out at the time of registration and when a serious adverse event occurs.

### Plans for dissemination

The results of this study will be published in peer-reviewed journals.

### Study status

We are currently recruiting patients.

### Discussion

The efficacy of ibandronate in vertebral fractures has been demonstrated in patients with postmenopausal osteoporosis. According to the BONE study, oral daily (2.5 mg) and intermittent ibandronate (between-dose interval of >2 months) intake reduced the risk of new morphometric vertebral fractures by 62%.<sup>17</sup> The DIVA study demonstrated the efficacy of intravenous ibandronate as a useful alternative to oral dosing,<sup>18</sup> and intravenous ibandronate was approved in Japan in 2013 after a phase II/III clinical study (the MOVER trial<sup>19</sup>). This study demonstrated the non-inferiority of 1 mg of

intravenous ibandronate to risedronate. At three years, the mean relative change in bone mineral density from baseline was 9.0% for the ibandronate group and 7.6% for risedronate groups.<sup>19</sup> Moreover, the rate of first new vertebral fractures was 11.6% in the ibandronate group and 13.2% in the risedronate group. Although the rates of acute-phase reaction were higher in the ibandronate group (11.2% in the ibandronate group vs. 4.9% in the risedronate group), severe gastrointestinal adverse events were lower in the ibandronate group (0.5% in the ibandronate group vs. 2.2% in the risedronate group). The efficacy of monthly oral ibandronate was evaluated by the MOBILE study,<sup>20</sup> which concluded that the monthly intake was at least as effective and well-tolerated as the daily ibandronate regimen in postmenopausal osteoporosis. The MOVEST study<sup>13</sup> involved a randomized trial of 100 mg of monthly oral ibandronate versus 1 mg of monthly intravenous ibandronate in a Japanese population and showed comparable mineral density of the lumbar spine after 12 months of treatment (5.22% [oral] vs. 5.34% [intravenous]). Subsequently, monthly oral ibandronate intake was approved in Japan in 2016. In a real-world setting, a post-marketing observational study of 1,025 Japanese people revealed that 49.7% of the patients were concomitantly prescribed active vitamin D drugs, and preferable results with combined therapy were suggested in terms of bone mineral density at one year (3.54% [ibandronate alone] vs. 5.74% [ibandronate + eldcalcitol]).<sup>21</sup>

To date, studies have reported that the intake of calcium gluconate,<sup>22</sup> vitamin D,<sup>2</sup> or bisphosphonate<sup>23</sup> is useful after gastrectomy. Despite this, a standard treatment has not been established. In Japan, Segawa *et al.*, reported that osteoporosis was recorded in 29.5% of patients after gastrectomy<sup>24</sup> and reported that being over 70 years of age, weight loss, and chemotherapy were risk factors for osteoporosis. Sugiyama *et al.*, reported that the rate of increase in lumbar bone mineral density was 9.3% at one year when oral alendronate was administered to patients after gastrectomy.<sup>23</sup> Hirota *et al.*, compared minodronate and eldcalcitol in post-operative patients with gastric cancer and the increase in mineral density of the lumbar spine was 4.52% in the minodronate group and 1.72% in the eldcalcitol group.<sup>25</sup> Similarly, Ha *et al.*, compared outcomes of administration of a weekly dose of alendronate (70 mg) + daily elemental calcium (500 mg) with cholecalciferol (1,000 IU) with those of administration of daily elemental calcium (500 mg) with cholecalciferol (100 IU) only. They reported a significantly smaller decrease in mineral density of the lumbar spine in patients who received alendronate and those who did not ( $-0.28 \pm 5.20$  vs.  $8.39 \pm 7.41$ , respectively).<sup>26</sup> Although it is difficult to integrate the results of these studies owing to the varied characteristics of patients after gastrectomy, methodology, and types of investigational drugs, there seem to be consistent positive effects on bone metabolism as a result of osteoporosis prophylaxis.

We should be aware of the disadvantages of bisphosphonate, including acute-phase reaction, general malaise, renal failure, joint pain, gastrointestinal symptoms, hypocalcemia, osteonecrosis of the jaw, and atypical femoral fracture.<sup>27</sup> However, according to the results of the MOVEST study,<sup>13</sup> there were no significant differences in adverse events between the oral intake and intravenous groups except for gastrointestinal symptoms, and we hypothesize that intravenous injection is appropriate for the management of post-gastrectomy patients. Considering the less variable bioavailability of intravenous ibandronate than the highly variable bioavailability of oral ibandronate,<sup>28</sup> especially in patients with malabsorption, a more stable concentration should be assured. In addition, a previous study reported that the completion rate of oral minodronate administration<sup>26</sup> was 77.5% in patients who underwent gastrectomy. This relatively low rate of compliance with drug use should be assessed further.

In conclusion, we plan to conduct a prospective study on the efficacy of ibandronate plus eldcalcitol in patients with gastric cancer after gastrectomy, focusing on different routes of administration. We believe that the results of this trial will conclusively identify a novel strategy for the post-gastrectomy treatment of osteoporosis in patients with gastric cancer.

#### Data availability

##### Underlying data

No data are associated with this article.

##### Extended data

Figshare: case report form.xlsx. <https://doi.org/10.6084/m9.figshare.20217278.v3>.<sup>29</sup>

#### Reporting guidelines

Figshare: SPIRIT checklist for 'Protocol for a randomized study of the efficacy of ibandronic acid plus eldcalcitol in patients with gastric cancer after gastrectomy: A comparative study of different routes of administration of ibandronic acid'. <https://doi.org/10.6084/m9.figshare.20217338.v1>.<sup>30</sup>

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).



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## Version 2

Reviewer Report 23 December 2023

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### Friederike Thomasius

Frankfurter Hormon Und Osteoporosezentrum, Frankfurt, Germany

No further comment, my general concern about the administration of an oral bisphosphonate in patients after gastrectomy remains.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Osteology, diagnosis of osteoporosis, Osteoporosis therapy, Osteoporosis Guideline

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 05 May 2023

<https://doi.org/10.5256/f1000research.147725.r172025>

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### Carlen Reyes

Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain

The authors have addressed all the queries so I have no further issues regarding the indexing of the protocol.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Osteoporosis, pharmacoepidemiology, bone fracture

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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Version 1

Reviewer Report 25 April 2023

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### Friederike Thomasius

Frankfurter Hormon Und Osteoporosezentrum, Frankfurt, Germany

#### Summary

Patients after gastrectomy due to Gastric cancer will be randomized into a single center, non blinded trial with two treatment options: Oral Ibandronate monthly plus eldecalcitol, or intravenous ibandronate monthly plus eldecalcitol.

The planned patients to be included patients cover the age between 20 and 85 years, patients with existing fractures and lowered BMD, the planned number of patients to be included in this study is 70 (35 per group), duration of the study 52 weeks.

#### Comments

The inclusion criteria should include a sufficient daily calcium intake which should be assessed with a standardized questionnaire, or due to known data of average calcium intake in the examined population, a calcium supplement should be provided

With regard to exclusion criteria the contraindications for ibandronic acid therapy are partially missing, and the following need to be added:

- inability to sit or stand in an upright position
- stenosis of the esophagus or achalasia
- hypersensitivity to Ibandronic acid

Target outcomes of bone metabolism markers should include CTX as one of the most examined parameters.

#### General comment

Choosing an oral Bisphosphonate as Osteoporosis therapy after gastrectomy needs more explanation. Due to the low bioavailability of oral Bisphosphonates, a gastrectomy and a change in the passage might negatively influence the absorption of the oral Ibandronate.

**Is the rationale for, and objectives of, the study clearly described?**

Yes

**Is the study design appropriate for the research question?**

Partly

**Are sufficient details of the methods provided to allow replication by others?**

Yes

**Are the datasets clearly presented in a useable and accessible format?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Osteology, diagnosis of osteoporosis, Osteoporosis therapy, Osteoporosis Guideline

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 01 May 2023

**Hisaki Aiba**

Thank you for your advices to this article. Based on your comments and other reviewers' comments, we will also modify the original protocols. We amended point-by-point according to your suggestions.

Summary: Patients after gastrectomy due to Gastric cancer will be randomized into a single center, non blinded trial with two treatment options: Oral Ibandronate monthly plus eldecacitol, or intravenous ibandronate monthly plus eldecacitol.

The planned patients to be included patients cover the age between 20 and 85 years, patients with existing fractures and lowered BMD, the planned number of patients to be included in this study is 70 (35 per group), duration of the study 52 weeks.

(Question 1) The inclusion criteria should include a sufficient daily calcium intake which should be assessed with a standardized questionnaire, or due to known data of average calcium intake in the examined population, a calcium supplement should be provided.

**(Response 1) Thank you for your comment. I included the questions of behavior of calcium intake and supplement. Also, we checked the baseline calcium values. (Section, "Schedule")**

(Question 2) With regard to exclusion criteria the contraindications for ibandronic acid

therapy are partially missing, and the following need to be added: inability to sit or stand in an upright position, stenosis of the esophagus or achalasia, hypersensitivity to Ibandronic acid.

**(Response 2) We added the following; inability to sit or stand in an upright position, stenosis of the esophagus or achalasia, hypersensitivity to Ibandronic acid on the description about contraindications. (Section, "Patients")**

(Question 3) Target outcomes of bone metabolism markers should include CTX as one of the most examined parameters.

**(Response 3) We depicted it. (Section, "Target outcomes")**

General comment

Choosing an oral Bisphosphonate as Osteoporosis therapy after gastrectomy needs more explanation. Due to the low bioavailability of oral Bisphosphonates, a gastrectomy and a change in the passage might negatively influence the absorption of the oral Ibandronate.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 11 April 2023

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**Carlen Reyes**

Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain

The authors describe a protocol of a randomized, active-controlled, nonblind study aimed to examine the efficacy of different ibandronic acid administration routes (oral versus iv) and its effects on bone metabolism in patients that have undergone gastric surgery for gastric cancer in an academic hospital in Japan. This is a very interesting study, well written, which will contribute to generate evidence regarding the best fracture prevention strategy in this population at risk.

The authors might wish to address the following suggestions:

**Major changes:**

1. The authors' state that the age of recruitment is from 20 to 85 years old. This age range is wide, and does not fully match the age of increased risk of gastric cancer or the age of increased risk of bone fracture. Given that usually people with gastric cancer are diagnosed in their 60s' and that the increased risk of fracture is mostly in people of at least 45 years old

(if considering postmenopausal women), including people of 20 years old might underestimate the real effect of ibandronic acid on bone. The authors should consider narrowing the population to focus on those who are at increased risk of the exposure and outcome.

2. In the exclusion criteria: “people with a high risk of osteonecrosis of the jaw”, the authors should state how is this going to be addressed or how is it going to be defined.
3. In the exclusion criteria: “patients who are considered inappropriate by the attending physician” this exclusion criteria should be qualified as it can include many conditions that could lead to a selection bias; i.e. physicians may be more prone to exclude patients with more comorbid conditions who are also those with an increased risk of bone fracture.
4. In the target outcome paragraph, the authors define the lumbar bone mineral density as the primary outcome. The presence of osteophytes and osteoarthritis interfere with the bone densitometry measurements, which makes it not a suitable surrogate of osteoporosis <sup>1,2</sup>. In fact, osteoporosis is recommended to be assessed only through hip densitometry (i.e. FRAX tool). Authors should consider placing hip densitometry as their primary outcome or assessing osteoarthritis in their evaluation given the increased prevalence of this disease especially in those >50 years old.
5. Safety paragraph: I am missing a list of adverse events to be assessed. This paragraph is too vague and a predefined list of outcomes (adverse events included and how they are going to be defined) should be clearly detailed.

#### Minor changes:

1. The inclusion criteria do not specify if the patients need to comply all of the conditions or just any of them.
2. The phrase “post-surgery duration of less than six months” is unclear; does it mean that only those that had a surgery in the last 6 months will be included? Please specify.
3. In the exclusion criteria: “patients with significant anorexia”, I think the term “significant” is not correct. I would suggest that the authors exclude those with a diagnosis of anorexia.

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#### Is the rationale for, and objectives of, the study clearly described?

Yes

#### Is the study design appropriate for the research question?

Partly

**Are sufficient details of the methods provided to allow replication by others?**

Partly

**Are the datasets clearly presented in a useable and accessible format?**

Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Osteoporosis, pharmacoepidemiology, bone fracture

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 01 May 2023

**Hisaki Aiba**

Thank you for your advices to this article. Based on your comments and other reviewers' comments, we will also modify the original protocols. We amended point-by-point according to your suggestions.

(Comment of reviewer 1) The authors describe a protocol of a randomized, active-controlled, nonblind study aimed to examine the efficacy of different ibandronic acid administration routes (oral versus iv) and its effects on bone metabolism in patients that have undergone gastric surgery for gastric cancer in an academic hospital in Japan. This is a very interesting study, well written, which will contribute to generate evidence regarding the best fracture prevention strategy in this population at risk.

The authors might wish to address the following suggestions:

Major changes:

(Question1) The authors' state that the age of recruitment is from 20 to 85 years old. This age range is wide, and does not fully match the age of increased risk of gastric cancer or the age of increased risk of bone fracture. Given that usually people with gastric cancer are diagnosed in their 60s' and that the increased risk of fracture is mostly in people of at least 45 years old (if considering postmenopausal women), including people of 20 years old might underestimate the real effect of ibandronic acid on bone. The authors should consider narrowing the population to focus on those who are at increased risk of the exposure and outcome.

**(Response1) This description is based on the PMDA approval of the ibandronic acid in Japan. We are not actually intended to use it for younger patients. Anyway, the age at least over 45 might be reasonable. So, we changed it (Abstract and Section, "Patient").**

(Question 2) In the exclusion criteria: "people with a high risk of osteonecrosis of the jaw",

the authors should state how is this going to be addressed or how is it going to be defined.

**(Response 2) The risk assessment of the osteonecrosis of the jaw is usually considered by examination of dentists. As local factors for the necrosis, chronic periodontitis, necessity of tooth extractions, poorly-fitting denture use should be checked before administration of bisphosphonate. Also, as the systemic factors, concurrent use of steroids, older age (above 65 years), and coexisting diagnosis of diabetes mellitus should be taken into account. Based on these factors, the dentists and clinicians in charge judge the risk and eligibility (Section, "Patient"). [Bansal H. Medication-related osteonecrosis of the jaw: An update. Natl J Maxillofac Surg. 2022 Jan-Apr;13(1):5-10.]**

(Question 3) In the exclusion criteria: "patients who are considered inappropriate by the attending physician" this exclusion criteria should be qualified as it can include many conditions that could lead to a selection bias; i.e. physicians may be more prone to exclude patients with more comorbid conditions who are also those with an increased risk of bone fracture.

**(Response 3) This phrase means the physician's judgement to permit for the clinical study will be affected several clinical setting of patients. Social problem, economical problem, or the characteristics of the patients will be taken into account. We substitute the information in detail. (Section, "Patient").**

(Question 4) In the target outcome paragraph, the authors define the lumbar bone mineral density as the primary outcome. The presence of osteophytes and osteoarthritis interfere with the bone densitometry measurements, which makes it not a suitable surrogate of osteoporosis. In fact, osteoporosis is recommended to be assessed only through hip densitometry (i.e. FRAX tool). Authors should consider placing hip densitometry as their primary outcome or assessing osteoarthritis in their evaluation given the increased prevalence of this disease especially in those >50 years old.

**(Response 4) Your comment is reasonable. I changed the description (Section, "Target outcome").**

(Question 5) Safety paragraph: I am missing a list of adverse events to be assessed. This paragraph is too vague and a predefined list of outcomes (adverse events included and how they are going to be defined) should be clearly detailed.

**(Response 5) Your comment is reasonable. We inserted several points which should be monitored. Also, we added the criteria for the evaluation of adverse events (Section, "Target outcome").**

Minor changes:

(Question 6) The inclusion criteria do not specify if the patients need to comply all of the conditions or just any of them.

**(Response 6) We inserted the description. (Section, "Patients").**



(Question 7) The phrase “post-surgery duration of less than six months” is unclear; does it mean that only those that had a surgery in the last 6 months will be included? Please specify.

**(Response 7) We inserted this criterion with the aim that the early osteoporosis treatment might be effective for the patients after gastrectomy. As you suggested, this phrase is unclear, thus, we changed the phrase as “patients less than six months after gastrectomy.” (Section, “Patients”).**

(Question 8) In the exclusion criteria: “patients with significant anorexia”, I think the term “significant” is not correct. I would suggest that the authors exclude those with a diagnosis of anorexia.

**(Response 8) The patients after gastrectomy sometimes experience the change in eating habits and lose weights. This condition might invoke the infringement of regular intake of drugs. Anyway I deleted “significant”. (Section, “Patients”).**

**Competing Interests:** No competing interests were disclosed.

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