Title: Vonoprazan study in patients with erosive esophagitis to evaluate long-term safety: A study to evaluate the safety of long-term administration of vonoprazan in maintenance treatment in patients with erosive esophagitis (EE)

NCT Number: NCT02679508

Protocol Approve Date: 10-Jun-2021

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

PROTOCOL

Evaluation of Long-term Safety of Maintenance Treatment with Vonoprazan in Patients with Erosive Esophagitis

Vonoprazan study **i**n patients with er**osi**ve esophagitis to evaluate **lon**g-term safety (VISION)

Protocol number	Vonoprazan-4003
Version Number	Version 5
Study drug:	Vonoprazan fumarate
Creation date	6/10/2021

Revision history

Date	Revision number	Applicable to
January 20, 2016	Version 1	All the study sites
September 17, 2019	Version 2	All the study sites
August 24, 2020	Version 3	All the study sites
November 10, 2020	Version 4	All the study sites
February 16, 2021	Version 4.1	All the study sites
June 10, 2021	Version 5	All the study sites

1.0 STUDY PRINCIPLES AND STUDY ADMINISTRATIVE INFORMATION

1.1 Clinical research Principals

- This study will be conducted as a "specified clinical research" based on the Clinical Trials Act (Act No. 16 of 2017) with the highest respect for the individual participants in accordance with the requirements of this protocol and also in accordance with the following: The ethical principles that have their origin in the Declaration of Helsinki.
- Clinical Trials Act (Act No. 16 of 2017)
- Guideline for Good Clinical Practice (ICH-E6) (hereinafter referred to as "ICH-GCP"). （just for a reference）
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 Clinical research System

This study will be conducted in the following system, in accordance with the protocol of the study, which was planned and designed by Takeda:

Representative investigator

[redacted]

Certified Review Board

[redacted]

Secondary Sponsor and the person in charge of supporting the research and development plan

Japan Medical Office, Japan Pharma Business Unit, Takeda

Takeda is responsible for the planning and design, and the representative investigator and Takeda are responsible for the implementation and management, and the results and

reporting of this study. A separate procedure describes the way how outsourcing providers involved in this study should be supervised.

Takeda shall pay the expenses* arising from the management of this study.

*: Takeda shall pay the expenses arising from operations at the research office, monitoring activities, operations at the registration and allocation center, statistical analyses, and audits to outsourcing providers involved in this study, in accordance with the Outsourcing Contract. To study sites, Takeda shall pay the expenses at the agreed amount with study sites, which are calculated based on a separate document, Research Expenses Calculation Standard.

Research Steering Committee

Chairperson (who concurrently serves as "the person who directs the research"):

[redacted]

Members:

[redacted]

The Research Steering Committee shall be composed of the chairperson and members of the committee, and Takeda. The representative investigator and the Research Steering Committee shall supervise implementation and reporting of the clinical research, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the protocol appropriately.

In addition, the terms used in this protocol are defined as follows:

Study site:

Medical institution where this clinical research will be conducted.

Collaborative study site:

A study site where this clinical research will be collaboratively conducted in accordance with the protocol

Investigator:

A physician who is engaged in implementing a specified clinical research and directing research-related duties at the study site which he/she belongs to.

Sub-investigator:

A physician who is engaged in implementing a part of research-related duties under the guidance of investigator at the study site.

Representative investigator:

A physician who is representative of investigators of more than one study site in case of multicenter study.Person in charge of supporting the research and development plan:

A person who clarifies the direction of the research as a whole, efficiently plans and operates a series of processes from the idea, strategy formulation to publication of results (or commercialization), supports the optimization of more than one necessitated clinical research, basic research, etc., and supports the creation of a framework of the most effective and efficient (optimized) clinical research plan based on the clinical development plan.

Person in charge of practical coordination and management:

A person who smoothly operates the clinical research based on the knowledge and means concerning the planned and efficient operational management of the clinical research.

Person who directs the research:

A person who procures research funds, etc. for the clinical research, and directs the clinical research.

Research Subject:

A person (including deceased individual) who corresponds any of the following descriptions:

(1) An individual on whom research is implemented(including an individual asked to be enrolled in the research); or

(2) An individual from whom existing specimen or information had arisen.

1.3 Contact Information on the Protocol

[redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Representative investigator: Junichi Akiyama, Center Hospital of the National Center for Global Health and Medicine **Secondary Sponsor and the person in charge of supporting the research and development plan:** Takeda	**Study drug:** Vonoprazan fumarate

Study title:

Vonoprazan study In patients with erosive esophagitis to evaluate long-term safety:
A study to evaluate the safety of long-term administration of vonoprazan in maintenance treatment in patients with erosive esophagitis (EE)

Protocol number: Vonoprazan-4003

Clinical research design:

This is a multicenter, open-label, randomized, parallel-group study to exploratorily evaluate the effect on gastric mucosal tissue and the safety of long-term administration of vonoprazan in maintenance treatment after healed EE, and the curative effect of vonoprazan versus lansoprazole in patients with EE.

Patients endoscopically diagnosed with EE of Los Angeles (LA) Classification Grades A to D at the start of treatment (Week 0 of the healing phase) will be randomly assigned to receive either vonoprazan 20 mg or lansoprazole 30 mg to be taken once daily for up to 8 weeks. Subjects with healed EE as confirmed endoscopically at Week 4 or 8 in the healing phase will enter the maintenance phase.
In the maintenance phase, the vonoprazan group and the lansoprazole group will be administered a starting dose of 10 mg and 15 mg, respectively, once daily up to 260 weeks.

If the investigator or sub-investigator judged the effect of vonoprazan 10 mg or lansoprazole 15 mg to be insufficient as the maintenance treatment of EE, vonoprazan and lansoprazole may be increased to 20 mg and 30 mg, respectively.

The research period will consist of two subperiods: healing phase in which patients with EE will receive treatment (for 4 or 8 weeks) and maintenance phase in which patients will receive maintenance treatment (for 260 weeks), and thus, a total of up to 268 weeks. The number of visits will be a maximum of 18 visits. Planned number of research subjects, as the number of research subjects for entry to the maintenance phase, will be 130 patients in the vonoprazan group and 65 patients in the lansoprazole group.
In addition to the final analysis using data up to the final VISIT, interim analysis using data up to the pre-defined VISIT will be performed once a year during the maintenance phase to evaluate the effect of long term administration of vonoprazan on gastric mucosal tissue as maintenance treatment in patients with recurrent/reactivated erosive esophagitis when data up to the pre-defined VISIT (Week 48 [VISIT M5], Week 108 [VISIT M10], Week 156 [VIST M12], and Week 204 [VIST M14] in the maintenance

<table>
<tr><td colspan="2">phase) is collected from all the subjects . The interim analysis is not intended to use decision whether to continue or terminate this study.</td></tr>
<tr><td colspan="2">Objective:
To exploratorily evaluate the effect on gastric mucosal tissue and the safety of long-term administration (260 weeks: 5 years) of vonoprazan 10 mg or 20 mg in patients receiving maintenance treatment after healed EE, and the curative effect of vonoprazan 20 mg versus lansoprazole in patients with EE.</td></tr>
<tr><td colspan="2">Study population:
Healing phase: Patients with EE
Maintenance phase: Patients included for maintenance treatment after healed EE</td></tr>
<tr><td>Planned number of research subjects:
As the number of research subjects for entry to the maintenance phase,
Vonoprazan group: 130 patients
Lansoprazole group: 65 patients</td><td>Number of study sites:
Approximately 30 sites</td></tr>
<tr><td>Dose and method of administration:
< Healing phase >
Vonoprazan group: Vonoprazan 20 mg orally administered once daily
Lansoprazole group: Lansoprazole 30 mg orally administered once daily
< Maintenance phase >
Vonoprazan group: Vonoprazan 10 mg or 20 mg orally administered once daily
Lansoprazole group: Lansoprazole 15 mg or30 mg orally administered once daily</td><td>Route of administration:
Oral</td></tr>
<tr><td>Duration of treatment:
Healing phase: 4 or 8 weeks
Maintenance phase: 260 weeks</td><td>Duration of evaluation:
Healing phase: 4 or 8 weeks
Maintenance phase: 260 weeks
Total: 264 or 268 weeks</td></tr>
<tr><td colspan="2">Criteria for inclusion:
Research subjects shall fulfill all of the following criteria to be included in this clinical research.
< At the start of healing phase >
1. Patients endoscopically diagnosed with EE of grades A to D by the LA Classification Grading System at the start of treatment (Week 0 of the healing phase).</td></tr>
</table>

2. Patients with *H. pylori* negative.
3. Patients who, in the opinion of the investigator or sub-investigator, are capable of understanding the content of the clinical research and complying with the protocol requirements.
4. Patients who can sign and date an informed consent form and information sheet prior to the conduction of the clinical research procedures.
5. Male or female patients aged 20 years or older at the time of informed consent.
6. Therapeutic category: Ambulatory.

< At the start of maintenance phase >

7. Patients who have endoscopically confirmed EE healing* (mucous membrane disorder is not observed) at completion of the healing phase (Week 4 or 8 of the healing phase).
   * Patients who are classified as grade 0 according to severity classification of EE (See Table 9.b)
8. Patients who have been determined to be appropriate as subjects for maintenance treatment of EE by the investigator or sub-investigator.

Criteria for exclusion:

Research subjects meeting any of the criteria below shall not be included in this research.

< At the start of healing phase >

1. Patients with concurrent peptic ulcer (except scarred stage) or Zollinger-Ellison syndrome.
2. Patients who received treatment with PPIs (including vonoprazan) within 4 weeks (Week -4 to Week 0) prior to the start of healing phase (Week 0 of the healing phase).
3. Patients with a history of *H. pylori* eradication.
4. Patients who have received surgery or treatment affecting gastroesophageal reflux (fundoplication or dilation for esophageal stenosis [excluding Schatzki's ring], etc.) .
5. Patients with an esophagus-related complication (eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal stenosis, etc.), a history of radiotherapy or cryotherapy of the esophagus, a caustic or physiochemical trauma (esophageal sclerotherapy, etc.). However, participants with Schatzki's ring (mucosal tissue ring around inferior esophageal sphincter) or Barrett's esophagus are allowed to be included.
6. Patients with clinically apparent hepatic impairment (e.g., AST or ALT levels at the time of informed consent: >1.5 times the upper limit of normal (ULN).
7. Patients with renal impairment or renal failure [creatinine clearance (CCr) <30 mL/min, etc.]
8. Patients with a history of hypersensitivity or allergy for PPIs.
9. Patients with a history of gastrectomy, gastrointestinal resection, or vagotomy.
10. Patients with a malignant tumor.
11. Patients who are pregnant, breast-feeding, possibly pregnant, or planning to become pregnant
12. Patients with one of the diseases listed under administration contraindication in the vonoprazan or

lansoprazole package insert.

13. Patients planning to take prohibited concomitant medications during the research period.
14. Patients participating in other clinical studies.
15. Patients who have been determined to be inappropriate as subjects in the study by the investigator or sub-investigator.

<At the start of maintenance phase >

16. Patients who have taken PPIs other than the study drug or the control drug during the healing phase.
17. Patients who have been determined to be inappropriate as subjects in the study by the investigator or sub-investigator.

Endpoints:

Primary endpoint:

- Histopathological examination of gastric mucosa

  Presence/absence of

  - ✧ Malignant transformation of epithelial cells
  - ✧ Parietal cell protrusion (PCP)/hyperplasia
  - ✧ Crypt epithelial hyperplasia
  - ✧ Endocrine cell proliferation
  - ✧ G-cell hyperplasia

Secondary endpoints:

Efficacy endpoints:

- Endoscopic EE recurrence rate
- EE healing rate at completion of the healing phase

Safety endpoints:

- Adverse events
- Endoscopic findings

Presence/absence of

- ✧ Fundic gland polyp
- ✧ Hyperplastic polyp

- ✧ Cobblestone mucosa
- ✧ Multiple white and flat elevated lesions
- ✧ Black spots

- Histological assessment of gastritis using the Sydney classification
  - ✧ Inflammation (mononuclear cell infiltration)
  - ✧ Active (neutrophil infiltration)
  - ✧ Atrophy
  - ✧ Intestinal metaplasia
  - ✧ *H. pylori*
- Incidence of gastric polyp

< Additional endpoints >

- Serum gastrin level
- Pepsinogen I and II levels
- Pepsinogen I/II ratio
- Serum chromogranin A level
- Laboratory test (AST, ALT, Fe, Mg, Ca, vitamin B_{12})
- Barrett's esophagus
- Esophageal hiatal hernia

Statistical method:

Percentage of "presence" of each of the variables in histopathological examination of gastric mucosa (presence/absence of malignant transformation of epithelial cells, parietal cell protrusion /hyperplasia, crypt epithelial hyperplasia, endocrine cell proliferation, G-cell hyperplasia) in the "safety analysis set in the maintenance phase" will be calculated by assessment time point and treatment group.

Rationale for the number of planned research subjects:

As the number of research subjects for entry to the maintenance phase,

Vonoprazan group: 130 subjects

Lansoprazole group: 65 patients

[**Rationale for the number of planned research subjects]**

In view of the withdrawal rate over 1 year (52 weeks) in the vonoprazan study conducted in Japan, and for integration of data regarding the effect of long-term administration on gastric mucosal tissue and further safety data in the vonoprazan group, the number of research subjects for entry to the maintenance phase, considering the feasibility, was determined to be a total of 130 as the number of randomized subjects in the vonoprazan group. Referring to the vonoprazan studies conducted in the past, at least approximately 100 patients, 50 patients, and 30 patients can be expected to be recruited in 1 year, 3 years, and 5 years, respectively. In this study, for the exploratory evaluation with lansoprazole as a control, the number of patients in the lansoprazole group was determined to be 65 with a 2:1 ratio between vonoprazan and lansoprazole groups.

These numbers were not determined on a statistical basis.

3.0 ABBREVIATION

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
COI	conflict of interest
CRO	contract research organization
EDC	electronic data capture
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
H. pylori	*helicobacter pylori*
ICH	International Conference on Harmonisation
LA classification	Los Angeles classification
MedDRA	Medical Dictionary for Regulatory Activities
PPI	proton pump inhibitor
TEAE	treatment emergent adverse event

4.0 INTRODUCTION

4.1 Background

The prevalence of erosive esophagitis (erosive GERD) in Japan, which used to be considered lower than that in the West, has reportedly been increasing since the late 1990s. [1)] This increase may be primarily due to westernization of diets and decreased prevalence of *H. pylori* in young people, which affect gastric acid secretion.

Erosive esophagitis (erosive GERD) is caused by reflux of gastric acid due to relaxation of the inferior esophageal sphincter, reduced esophageal clearance function, impaired esophageal mucosal defense mechanisms, etc. Severity of erosive esophagitis is correlated with the duration of esophageal exposure to acid and pH of refluxed gastric contents. In the treatment of erosive esophagitis, therefore, drugs that can suppress gastric acid secretion more strongly and more continuously may be more effective in healing it.

The first choice for initial treatment of erosive esophagitis is proton pump inhibitors (PPIs), which suppress gastric acid secretion effectively. PPIs are highly effective for erosive esophagitis, with high healing rates known to range from 80% to 90% at Week 8 of treatment [2)]; however, it has been reported that healing rates at Week 8 of PPI treatment were lower in patients with endoscopically more severe disease at baseline. [3)] In addition, erosive esophagitis is known to often recur, and repeated healing and recurrence may result in increased risk of complications such as Barrett's esophagus and esophageal stenosis. For prevention of recurrent erosive esophagitis, continuous drug therapy (maintenance treatment) is important; in particular, the Guidelines for Management of Gastroesophageal Reflux Disease published by the Japanese Society of Gastroenterology recommend aggressive maintenance treatment for severe erosive esophagitis. Maintenance treatment is intended to prevent recurrence and is therefore administered on a long-term basis in some patients. Accordingly, it is very important to establish the safety of long-term maintenance treatment.

It has been concerned that conventional PPIs, especially when used for a long period of time, may induce carcinoid tumor due to increased serum gastrin, impair absorption of vitamins, and accelerate the progression of atrophic gastritis by suppressing gastric acid secretion; however, long-term outcomes in and outside Japan show that long-term use was associated with few clinical problems. [4)5)]

On the other hand, vonoprazan is an acid suppressant in a new category that suppresses gastric acid secretion more strongly and more continuously than conventional PPIs by reversibly inhibiting H^+, K^+ -ATPase in the final stage of acid secretion in a K^+ -competitive manner. In a 1-year long-term clinical research of vonoprazan, serum gastrin levels tended to increase, as did with PPIs; however, serum gastrin had no effect on neuroendocrine cells in the fundic glands or no great effect on neuroendocrine cells (Grimelius-positive cells, chromogranin A-positive cells, and synaptophysin-positive cells) in the fundic gland. These results indicate that vonoprazan is a new acid suppressant with a safety profile similar to that of conventional PPIs. However, since there have been few reports of long-term treatment with vonoprazan, safety data collected during long-term treatment will be useful in maintenance treatment of erosive esophagitis.

The present study will be conducted in patients with erosive esophagitis to evaluate the effect on gastric mucosa and safety of vonoprazan 10 mg or 20 mg given for 260 weeks (5 years) as maintenance treatment on an exploratory basis with lansoprazole as control, with an aim to evaluate the long-term safety of vonoprazan in patients under maintenance treatment.

4.2 Rationale for the proposed research

This study will be conducted in patients with recurrent/reactivated erosive esophagitis (EE) to evaluate the effect on gastric mucosa and safety of vonoprazan 10 mg or 20 mg given for 260 weeks as maintenance treatment or for up to 268 weeks including the healing phase, with an aim to provide long-term maintenance treatment of EE and contribute to prevention of recurrence.

Meanwhile, this study is not planned as an additional pharmacovigilance activity in the risk management plan of vonoprazan.

5.0 RESEARCH OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the effect on gastric mucosa and safety of long-term treatment (260 weeks: 5 years) with vonoprazan 10 mg or 20 mg in patients under maintenance treatment of recurrent/reactivated EE as well as the healing efficacy of vonoprazan 20 mg in patients with EE on an exploratory basis with lansoprazole as control

5.2 Definition of endpoints

5.2.1 Primary endpoint

- Gastric mucosa histopathology
  - ✧ Presence or absence of malignant alteration of epithelial cells
  - ✧ Presence or absence of prominence/hyperplasia of wall cells
  - ✧ Presence or absence of hyperplasia of crypt epithelial cells
  - ✧ Presence or absence of proliferation of endocrine cells
  - ✧ Presence or absence of hyperplasia of G cells

5.2.2 Secondary endpoints

Efficacy endpoints

- Endoscopic EE recurrence rate
- EE healing rate at the end of the healing phase

Safety endpoints

- Incidence of adverse events
- Endoscopic findings
  - ✧ Presence or absence of fundic gland polyp
  - ✧ Presence or absence of hyperplastic polyp
  - ✧ Presence or absence of cobblestone mucosa
  - ✧ Presence or absence of multiple white flat elevation
  - ✧ Presence or absence of black spots

- Histological evaluation of gastritis according to the Sydney classification
  - ✧ Inflammation (mononuclear infiltration)
  - ✧ Activity (neutrophilic infiltration)
  - ✧ Atrophy
  - ✧ Intestinal metaplasia
  - ✧ *H. pylori*
- Incidence of gastric polyp

5.2.3 Additional endpoints

- Serum gastrin level
- Pepsinogen I/II levels
- Pepsinogen I/II ratio
- Serum chromogranin A level
- Laboratory test (AST, ALT, Mg, Fe, Ca, and vitamin B_{12})
- Barrett's esophagus
- Esophageal hiatal hernia

6.0 CLINICAL RESEARCH DESIGN

6.1 Clinical research design

<Clinical research design>

This is a multicenter, open-label, randomized, parallel-group study to exploratorily evaluate the effect on gastric mucosal tissue and the safety of long-term administration of vonoprazan in maintenance treatment after healed EE, and the curative effect of vonoprazan versus lansoprazole in patients with EE.

Patients endoscopically diagnosed with EE of Los Angeles (LA) Classification Grades A to D at the start of treatment (Week 0 of the healing phase) will be randomly assigned to receive either vonoprazan 20 mg or lansoprazole 30 mg to be taken once daily for up to 8 weeks. Subjects with healed EE as confirmed endoscopically at Week 4 or 8 in the healing phase will enter the maintenance phase.

In the maintenance phase, the vonoprazan group and the lansoprazole group will be administered a starting dose of 10 mg and 15 mg, respectively, once daily up to 260 weeks.

If the investigator or sub-investigator judged the effect of vonoprazan 10 mg or lansoprazole 15 mg to be insufficient as the maintenance treatment of EE, vonoprazan and lansoprazole may be increased to 20 mg and 30 mg, respectively.

The research period will consist of two subperiods: healing phase in which patients with EE will receive treatment (for 4 or 8 weeks) and maintenance phase in which patients will receive maintenance treatment (for 260 weeks), and thus, a total of up to 268 weeks. The number of visits will be a maximum of 18 visits. Planned number of research subjects, as the number of research subjects for entry to the maintenance phase, will be 130 patients in the vonoprazan group and 65 patients in the lansoprazole group.

In addition to the final analysis using data up to the final VISIT, interim analysis using data up to the pre-defined VISIT will be performed once a year during the maintenance phase to evaluate the effect of long term administration of vonoprazan on gastric mucosal tissue as maintenance treatment in patients with recurrent/reactivated erosive esophagitis when data up to the pre-defined VISIT (Week 48 [VISIT M5], Week 108 [VISIT M10], Week 156 [VIST M12], and Week 204 [VIST M14] in the maintenance phase) is collected from all the subjects. The

interim analysis is not intended to use decision whether to continue or terminate this study.

<Study treatment>

1. Drugs to be administered

   Vonoprazan or lansoprazole shall be administered.

2. Start of study drug administration and dose

   After acquisition of informed consent, research subjects determined eligible for the study in accordance with the inclusion and exclusion criteria shall enter the healing phase to orally receive vonoprazan 20 mg (once daily) or lansoprazole 30 mg (once daily).

   Research subjects with healed EE as confirmed endoscopically at the end of the healing phase (Week 4 or 8 in the healing phase) shall enter the maintenance phase to orally receive vonoprazan 10 mg (once daily) or lansoprazole 15 mg (once daily).

   Research subjects with no endoscopic healing of EE at the end of the healing phase (Week 8 in the healing phase) shall complete the study without entering the maintenance phase.

   If the investigator or sub-investigator determines that maintenance treatment of EE with vonoprazan 10 mg or lansoprazole 15 mg is not sufficiently effective in the maintenance phase, the dose may be increased to vonoprazan 20 mg or lansoprazole 30 mg. There will be no criteria for dose reduction.

3. Duration of treatment

   Healing phase: up to 8 weeks

   Maintenance phase: 260 weeks

<Planned duration of participation and number of visits for research subjects>

In this study, the duration of the study will be a maximum of 268 weeks, including the 8-week healing phase and the 260-week maintenance phase. During the healing phase, research subjects shall visit the study site at the start (Week 0) and end [(Week 4) (Week 8 for subjects with no endoscopic healing of EE at Week 4 in the healing phase)] of the healing phase.

Research subjects with healed EE as confirmed endoscopically at the end of the healing phase shall enter the maintenance phase and visit the study site every 12 weeks up to Week 108 in the maintenance phase. After that, research subjects visit the study site every 24 weeks up to Week 228 in the maintenance phase and the final VISIT is the end of the maintenance phase (Week 260). The number of visits will be a maximum of 18, including a maximum of 3 in the healing phase and 16 in the maintenance phase.

<Planned number of research subjects>

As the number of research subjects for entry to the maintenance phase,

Vonoprazan group 130 subjects

Lansoprazole group 65 subjects

<Number of study sites>

Approximately 30 sites

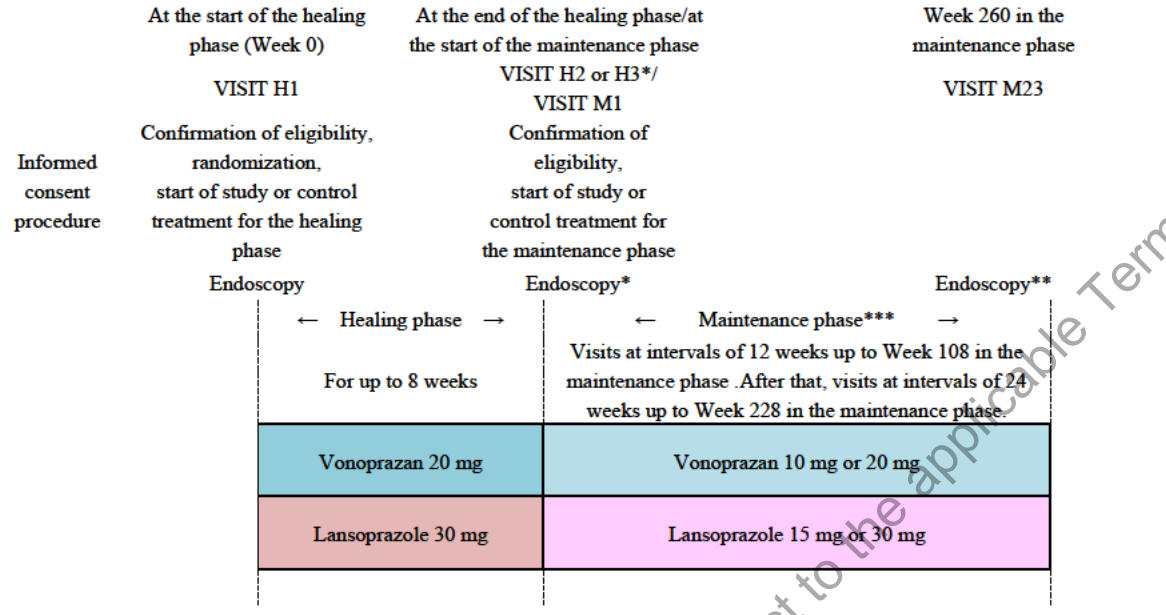
Figure 6 (a) shows a schematic of the clinical research design. Refer to [redacted] for schedule of examinations, observations, and assessments.

<Outline of clinical research>

Healing phase: 4 or 8 weeks

Maintenance phase: 260 weeks

Number of visits: up to 18



* For research subjects with no healing at Week 4 in the healing phase, healing shall be determined at Week 8 in the healing phase.
** After the start of the maintenance phase, endoscopy shall be performed at Weeks 48, 108, 156, 204, and 260 in the maintenance phase.
*** The interim analysis using data up to the pre-defined VISIT will be performed once a year during the maintenance phase to evaluate the effect of long term administration of vonoprazan on gastric mucosal tissue as maintenance treatment in patients with recurrent/reactivated erosive esophagitis when data up to the pre-defined VISIT (Week 48 [VISIT M5], Week 108 [VISIT M10], Week 156 [VIST M12], and Week 204 [VIST M14] in the maintenance phase) is collected from all the subjects.

Figure 6 (a) Outline of clinical research design

6.2 Rationale for the clinical research design

<Rationale>

Since the objective of this study is to exploratorily evaluate the effect on gastric mucosal tissue and the safety of vonoprazan administered at a dose of 10 mg or 20 mg once daily for up to 268 weeks throughout the treatment and maintenance phases with lansoprazole as control, it is designed as a multicenter, open-label, randomized, parallel-group study.

<Rationale for the dose and administration method>

Vonoprazan 20 mg or lansoprazole 30 mg shall be orally administered once daily to patients with EE in accordance with the package insert.

Vonoprazan 10 mg or 20 mg, or lansoprazole 15 mg or 30 mg shall be orally administered once daily to patients with recurrent/reactivated EE in accordance with the package insert.

<Rationale for the planned number of research subjects>

Refer to Section 13.3.

6.3 Premature termination of entire clinical research or premature termination of clinical research at a study site

6.3.1 Criteria for premature termination of entire clinical research

The representative investigator, the person who directs the research, and Takeda should immediately discontinue the study when at least one of the following criteria is applicable:

- When new information or other evaluation on the safety or efficacy of the study drug or control drug becomes available that shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for research subject participation in the study.
- When there is serious deviation from the Clinical Trials Act or ICH-GCP that may threaten safety of the research subjects.

6.3.2 Criteria for premature termination of study sites

Termination of involvement of a study site in the study may be requested prematurely at the discretion of the representative investigator, the person who directs the research, or Takeda if the entity (e.g., investigator) is found in significant violation of the Clinical Trials Act protocol, or contractual agreement, or is unable to ensure proper conduct of the research.

6.3.3 Procedures for clinical research suspension and premature termination of entire clinical research or study at a study site

In the event that the representative investigator, the person who directs the research, Takeda, or the certified review board decides to prematurely suspend or terminate the entire clinical research or clinical research at a study site, a study-specific procedure in accordance with the Clinical Trials Act shall be discussed among the representative investigator, the person who directs the research, and Takeda , and its discussion results shall be presented. The procedure shall be followed by the applicable study sites during the course of clinical research suspension or premature termination.

6.4 Procedures for protocol revision

If the protocol needs to be revised, the representative investigator, the person who directs the research, and Takeda shall consider and decide whether to revise the protocol. The investigator of each study site shall be informed of the details of each protocol revision after obtaining approval from the certified review board. Investigators shall confirm the content of the revision of the protocol and submit a letter of agreement to Takeda as evidence of agreement with the protocol revision.

The protocol shall be revised only when it meets the following criteria, and not be revised for minor changes that do not meet the following criteria.

[Protocol revision is required in the following cases:]

1. Change or addition of objectives;
2. Change in or addition of efficacy or safety evaluation methods;
3. More frequent or additional laboratory tests for which research subjects incur additional expenses or changes in laboratory test methods;
4. Change in dose (including adding an additional treatment group);
5. Significant change in or addition of inclusion and/or exclusion criteria;
6. Change in the planned number of research subjects;
7. Change in plans or in description of the protocol due to serious adverse events or other reasons; and
8. Change which is considered as a significant change, as a result of discussion among the representative investigator, the person who directs the research, and Takeda.

Upon notification, the investigator at each study site shall obtain approval from the supervisor of the study site based on review results of the certified review board. according to institutional regulations.

7.0 SELECTION AND WITHDRAWAL CRITERIA OF RESEARCH SUBJECTS

Before the start of the healing phase and the start of maintenance phase, the research subject's data, including test results, should be checked against all of the inclusion/exclusion criteria.

7.1 Criteria for inclusion

Research subjects shall fulfill all of the following criteria to be included in this clinical research.

<At the start of healing phase>

1. Patients endoscopically diagnosed with EE of grades A to D by the LA Classification Grading System at the start of treatment (Week 0 of the healing phase).
2. Patients with *H. pylori* negative.
3. Patients who, in the opinion of the investigator or sub-investigator, are capable of understanding the content of the clinical research and complying with the protocol requirements.
4. Patients who can sign and date an informed consent form and information sheet prior to the conduction of the clinical research procedures.
5. Male or female patients aged 20 years or older at the time of informed consent
6. Therapeutic category: Ambulatory.

<At the start of maintenance phase>

7. Patients who have endoscopically confirmed EE healing* (mucous membrane disorder is not observed) at completion of the healing phase (Week 4 or 8 of the healing phase).

   * Patients who are classified as grade 0 according to severity classification of EE (See Table 9.b).

8. Patients who have been determined to be appropriate as subjects for maintenance treatment of EE by the investigator or sub-investigator.

[Rationale for the inclusion criteria]

1.3.4.6. - 8. These were set as essential conditions for the clinical research.

2. The Japanese Guidelines for the Management of *Helicobacter Pylori* Infection in 2009 [6] recommend eradication of *H. pylori* for people infected with *H. pylori*, with no exception for those with erosive esophagitis. On the grounds that eradication of *H. pylori* should precede treatment of EE, therefore, this criterion was set.

5. This was set to allow for separate assessment of male/female. The lower age limit was set to 20 years to allow patients to make a voluntary decision regarding their participation in this clinical research.

7.2 Criteria for exclusion

Research subjects meeting any of the criteria below shall not be included in this research.

<At the start of healing phase>

1. Patients with concurrent peptic ulcer (except scarred stage) or Zollinger-Ellison syndrome.
2. Patients who received treatment with PPIs (including vonoprazan) within 4 weeks (Week -4 to Week 0) prior to the start of healing phase (Week 0 of the healing phase).
3. Patients with a history of *H. pylori* eradication.
4. Patients who have received surgery or treatment affecting gastroesophageal reflux (fundoplication or dilation for esophageal stenosis [excluding Schatzki's ring], etc.).
5. Patients with an esophagus-related complication (eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal stenosis, etc.), a history of radiotherapy or cryotherapy of the esophagus, a caustic or physiochemical trauma (esophageal sclerotherapy, etc.). However, participants with Schatzki's ring (mucosal tissue ring around inferior esophageal sphincter) or Barrett's esophagus are allowed to be included.
6. Patients with clinically apparent hepatic impairment (e.g., AST or ALT levels at the time of informed consent: >1.5 times the upper limit of normal (ULN).

7. Patients with renal impairment or renal failure [creatinine clearance (CCr) <30 mL/min, etc.]
8. Patients with a history of hypersensitivity or allergy for PPIs.
9. Patients with a history of gastrectomy, gastrointestinal resection, or vagotomy.
10. Patients with a malignant tumor.
11. Patients who are pregnant, breast-feeding, possibly pregnant, or planning to become pregnant.
12. Patients with one of the diseases listed under administration contraindication in the vonoprazan or lansoprazole package insert.
13. Patients planning to take prohibited concomitant medications during the research period.
14. Patients participating in other clinical studies
15. Patients who have been determined to be inappropriate as subjects in the study by the investigator or sub-investigator.

<At the start of maintenance phase>

16. Patients who have taken PPIs other than the study drug or the control drug during the healing phase.
17. Patients who have been determined to be inappropriate as subjects in the study by the investigator or sub-investigator.

[Rationale for the exclusion criteria]

1.4. - 10. These were set in consideration of safety of the research subjects.
2.16. This was set because it would affect pharmacometrics.
3. This was set to eliminate any effect of *H. pylori* infection or eradication of *H. pylori* on gastric mucosa.
11. - 15.17. These were set as fundamental items for the research.

7.3 Prohibited concomitant drugs

The following drugs should not be used concomitantly with the study drug or control drug during the study:

1. Drugs with which vonoprazan or lansoprazole should not be used concomitantly according to the package insert.
2. PPIs other than the study drug or control drug.
    - Omeprazole
    - Esomeprazole
    - Rabeprazole, etc.

[Rationale for the prohibited concomitant drugs]

1. These were set in consideration of safety of the research subjects.
2. These were set because they would affect pharmacometrics.

7.4 Research subject management

The investigator and sub-investigator shall instruct research subjects to adhere to the following throughout the research period:

1. Adhere to the instructions or restrictions prescribed in the research period (compliance with study or control treatment, prohibited concomitant drugs).
2. Inform the investigator or sub-investigator of any planned treatment by another physician. Promptly report any treatment done by another physician.
3. Visit the study site as scheduled to undergo physical examination or other specified tests. Cancel an appointment for study visit in a timely manner if applicable.
4. Visit the study site after at least 10 hours of fasting when endoscopy or laboratory test (e.g., serum gastrin level, pepsinogen I/II levels, Fe, vitamin B_{12}) is scheduled. Visit the study site without taking the study drug or control drug.
5. Avoid excessive eating or drinking, excessive diet change (e.g., change to extremely high-fat diet), and excessive exercise throughout the research period.

7.5 Criteria for discontinuation or withdrawal of a research subject

The investigator or sub-investigator shall record the main reason for discontinuation of protocol treatment on the case report form (CRF) according to the classification described below. Refer to Section 9.1.18 for research subjects who withdraw from the research before randomization.

1. **Adverse event**
   When the research subject had an adverse event that requires withdrawal of the research subject from the study because continued participation in the study would impose an unacceptable risk to the research subject's health, or when the research subject is unwilling to continue study participation because of the adverse event.
2. **Major protocol deviation**
   When it is discovered after randomization that a research subject does not meet the eligibility criteria or is not adhering to the protocol, and continued participation in the research would impose an unacceptable risk to the research subject's health.
3. **Lost to follow-up**
   When the research subject failed to make visits and could not be contacted. The attempts that were made to contact the research subject shall be recorded in the source documents.
4. **Voluntary termination**
   When the research subject wishes to withdraw from the research. The reason for discontinuation shall be recorded on the CRF when it is clarified.

   Note: Every effort shall be made to clarify the reason for voluntary termination (discontinuation due to an adverse event is not classified into "voluntary termination").
5. **Research termination**
   When the representative investigator, the person who directs the research, Takeda, the certified review board, or the regulatory authority has decided to terminate the study. Refer to Section 6.3.1 for details.
6. **Pregnancy**
   When a female research subject is found to be pregnant.

   Note: Research participation shall be immediately discontinued when pregnancy is known. Refer to Section 9.1.17.
7. **Lack of efficacy**
   When efficacy of the study drug or control drug is not evident and continuation of the research may pose an unacceptable risk to the research subjects in the opinion of the investigator or sub-investigator.

8. **Others**

When the investigator or sub-investigator decides to withdraw the research subject from the study for any other reason.

Note: The specific reasons should be recorded on the CRF.

7.6 Procedures for discontinuation of individual research subjects

The investigator or sub-investigator shall terminate a research subject's research participation when the research subject meets the criteria described in Section 7.5. Individual research subjects may discontinue their research participation without giving a reason at any time during the research. Should a research subject's participation be discontinued, the primary reason for termination shall be recorded on the CRF by the investigator or sub-investigator. In addition, efforts shall be made to perform all tests/observations/evaluations scheduled at the time of discontinuation.

8.0 RESEARCH TREATMENT

This section indicates the treatment regimen of this clinical research. Information on all treatment regimens prescribed in the protocol will be stated. See the latest package insert for details and handling of each drug.

8.1 Study drug or control drug

Study drug:

Generic name: vonoprazan fumarate [JAN]

Chemical name: 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine monofumarate

Control drug:

Generic name: lansoprazole [JAN]

Chemical name:
(*RS*)-2-({[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl) benzimidazole

8.1.1 Dose and administration method

The investigator or sub-investigator shall orally administer the study drug or control drug to research subjects as shown in Table 8.a.

In the healing phase, vonoprazan 20 mg or lansoprazole 30 mg shall be orally administered once daily for 4 or 8 weeks.

In the maintenance phase, vonoprazan 10 mg or lansoprazole 15 mg shall be orally administered as the initial dose once daily for 260 weeks. If vonoprazan 10 mg or lansoprazole 15 mg is not sufficiently effective, the dose may be increased to vonoprazan 20 mg or lansoprazole 30 mg, which shall also be orally administered once daily.

Research subjects shall be instructed to visit the study site for this study without taking the study drug or control drug throughout the healing phase and maintenance phase.

At the start of the healing phase (VISIT H1), research subjects who enter the healing phase shall be administered the study drug or control drug for the day after the completion of tests/observations/evaluations and then released from the study site.

Research subjects with healed EE as confirmed endoscopically at Week 4 in the healing phase (VISIT H2) shall complete the study or control treatment for the healing phase. Research subjects with no healing shall be administered the study drug or control drug for the day and then released from the study site.

Research subjects with healed EE as confirmed endoscopically at Week 8 in the healing phase (VISIT H3) shall complete the study or control treatment for the healing phase. Research subjects with no healing shall complete this study and then receive treatment in accordance with normal medical practice.

At the start of the maintenance phase (VISIT M1), research subjects who enter the maintenance phase shall be administered the study drug or control drug for the day after the completion of tests/observations/evaluations and then released from the study site.

Likewise at Week 12 in the maintenance phase (VISIT M2) and subsequent study visits, research subjects shall be administered the study drug or control drug for the day after the completion of tests/observations/evaluations and then released from the study site.

Table 8 (a) Treatment group and administration method

Healing phase		
Treatment group	Dose	Administration method
Vonoprazan group	Vonoprazan 20 mg	Orally administered once daily
Lansoprazole group	Lansoprazole 30 mg	Orally administered once daily

Maintenance phase		
Treatment group	Dose	Administration method
Vonoprazan group	Vonoprazan 10 mg as the initial dose and adjusted to vonoprazan 10 mg or 20 mg	Orally administered once daily
Lansoprazole group	Lansoprazole 15 mg as the initial dose and adjusted to lansoprazole 15 mg or 30 mg	Orally administered once daily

<Criteria for dose change>

If the investigator or sub-investigator determines that maintenance treatment of EE with vonoprazan 10 mg or lansoprazole 15 mg is not sufficiently effective during the

maintenance phase, the dose may be increased to vonoprazan 20 mg or lansoprazole 30 mg. There will be no criteria for dose reduction.

Any dose change shall be recorded with dates of administration at the altered dose on the CRF.

Research subjects for whom the dose is changed shall be administered the study drug or control drug for the day and then released from the study site.

<Orally disintegrating tablet>

Lansoprazole may be administered in the form of orally disintegrating tablet instead of capsule.

8.1.2 Overdose of the study drug

Overdose is defined as intentional or accidental administration of the study drug or control drug at a higher dose than that specified in the protocol, either by a health professional or by the research subject.

To consistently collect important safety information about overdose, the investigator or sub-investigator shall record all cases of overdose on the "Overdose" page of the CRF, irrespective of the presence or absence of accompanying adverse event. Adverse events associated with overdose shall be recorded on the "Adverse events" page of the CRF, in accordance with the procedures described in Section 10.0, "ADVERSE EVENTS."

In addition, serious adverse events associated with overdose shall be recorded in accordance with the procedures described in Section 10.2.2, "Collection and reporting of SAEs."

In the event of overdose, the investigator or sub-investigator shall treat the subject as required based on symptoms.

8.2 Allocation of the study drug and administration procedure

The investigator or sub-investigator shall access the web subject registration system for assignment of research subjects. On that occasion, the investigator or the designee shall notify necessary information for assignment such as research subject ID codes. Subsequently, the drug to be administered to each research subject shall be notified via the web registration system. The investigator or sub-investigator shall prescribe the study drug or control drug according to the notification and record the drug information on the CRF of each research subject.

8.3 Preparation and storage of allocation list

The allocation responsible person (designated by Takeda) shall create an allocation list and manage allocation information. Information on the allocation shall be kept in a safe place and shall not be available to anyone other than authorized persons, to secure independency from the clinical research.

9.0 CLINICAL RESEARCH PROTOCOL

9.1 Research procedures

The investigator or sub-investigator shall collect data in accordance with the procedure below. The same investigator or sub-investigator shall perform tests/observations/evaluation of research subjects, in principle. The study schedule is provided in [redacted].

9.1.1 Informed consent procedure

The procedures for obtaining informed consent are described in Section 15.3.

Consent shall be obtained from the research subject before initiation of research procedures.

Research subject ID code shall be given to each research subject from whom informed consent has been acquired. The research subject ID code shall be used throughout the research period and shall not be changed.

9.1.2 Demographic data, medical history, and previous therapeutic drugs

Demographic data shall be collected regarding date of birth, gender, smoking history, drinking history, and consumption of caffeine-containing beverage.

Medical history data shall be collected regarding clinically problematic diseases or symptoms that disappeared or were terminated within 1 year from the start of the healing phase. When the symptoms or disease persists, it shall be considered as a concurrent disease (Refer to Section 9.1.7).

- EE
- Other upper gastrointestinal diseases (non-erosive gastroesophageal reflux disease, gastric ulcer, and duodenal ulcer) and treatments

Previous therapeutic drug data shall be collected regarding the following drugs used within 12 weeks before the start of the healing phase and that are related to criteria for eligibility and assessment of efficacy/safety in terms of drug name (trade name or generic name) and treatment end date.

- PPIs (including vonoprazan)

9.1.3 Physical examination

All subsequent physical examinations after the start of the healing phase shall be assessed for clinically significant changes from the baseline examination.

9.1.4 Weight, height, and BMI

Body weight and height shall be measured. Takeda shall calculate the BMI using the following formula:

Body Mass Index: $BMI = \text{weight (kg)} / (\text{height (m)})^2$

Height shall be measured to the nearest whole number in centimeters. Body weight shall be measured to one decimal place in kilograms. The result of BMI shall be shown to one decimal place.

[Example:

Height = 176 cm, weight = 79.2 kg, BMI = $79.2/1.76^2 = 25.6$ kg/m^2]

9.1.5 Vital signs

For vital signs, blood pressure in sitting position (after resting for ≥ 5 minutes) and pulse rate (bpm) shall be measured.
When timing for the vital signs measurement overlaps with blood collection, priority shall be given to blood collection, and the vital signs shall be measured within 30 minutes before or after the blood collection.

9.1.6 Concomitant drug

Concomitant drugs are all drugs to be given in addition to the study drug or control drug. Drugs prescribed by doctors or the over-the-counter medicines purchased by the research subjects shall be included. At every hospital visit of the research subject, the status of use (drug name, route of administration, healing phase) of the drugs (including vitamin compound, over-the-counter medication, and Chinese medicine) used, other than the study drug or control drug, from the start of the healing phase to the completion of the clinical research shall be monitored.

9.1.7 Concurrent disease

A concurrent disease is defined as a disease or symptom that is present at the start of the healing phase. Clinically problematic laboratory test data and abnormal physical examination findings observed up to immediately before the start of the healing phase

shall be considered as a concurrent disease at the discretion of the investigator or sub-investigator. The content of concurrent disease (diagnosis) shall be investigated.

9.1.8 Laboratory tests

The laboratory tests listed below shall be performed. Blood samples shall be collected under fasted conditions (after at least 10 hours of fasting) preferably at the same time of the day for each research subject. Analysis shall be performed at the laboratory test measurement institution (refer to the attached sheet).

The investigator or sub-investigator shall evaluate and keep the reported laboratory test results.

Table 9 (a) Laboratory tests

Blood test
AST
ALT
Fe
Mg
Ca
Vitamin B_{12}

Close observation should be made, and if any hepatic abnormality is observed, such appropriate measures as discontinuation of study drug or control drug should be taken.

When ALT or AST is > 3 times the upper limit of normal (ULN), a reexamination (at least ALP, ALT, AST, total bilirubin, and γ-GTP) shall be performed as soon as possible.

(Refer to Sections 7.5 and 10.2.3)

When ALT or AST is > 3 times the upper limit of the reference value two times sequentially, the investigator or sub-investigator shall contact Takeda to discuss additional examination, detailed monitoring, discontinuation of treatment with the study drug or control drug, advisability of continued study treatment, detailed information of the research subjects, and/or factors other than the study drug or control drug.

The investigator shall keep laboratory test reference values, including the historical data.

9.1.9 Serum gastrin level

Serum gastrin level shall be measured. Blood samples for serum gastrin (collected together with those for laboratory tests) shall be collected according to the clinical research schedule ([redacted]).

Blood samples shall be collected under fasted conditions (after at least 10 hours of fasting) preferably at the same time of the day for each research subject. Analysis shall be performed at the laboratory test measurement institution (refer to the attached sheet).

9.1.10 Pepsinogen I/II levels and serum chromogranin A level

Pepsinogen I/II levels (pepsinogen I level, pepsinogen II level, and pepsinogen I/II ratio) and serum chromogranin A level shall be measured. Blood samples for pepsinogen I/II and serum chromogranin A (collected together with those for laboratory tests) shall be collected according to the clinical research schedule ([redacted]).

Blood samples shall be collected under fasted conditions (after at least 10 hours of fasting) preferably at the same time of the day for each research subject. Analysis shall be performed at the laboratory test measurement institution (refer to the attached sheet).

9.1.11 *H. pylori* urea breath test

Information on *H. pylori* infection (positive, negative), which may affect the development of EE and the gastric mucosa, shall be collected in *H. pylori* urea breath test to determine the eligibility for this study. *H. pylori* urea breath test shall be performed according to the clinical research schedule ([redacted]).

9.1.12 CYP2C19 genotype testing

CYP2C19 genotype testing shall be performed to collect information on the CYP2C19 genotype [EM (**1/*1*, **1/*2*, **1/*3*), PM (**2/*2*, **2/*3*, **3/*3*)], which affects the kinetics of lansoprazole in blood. Blood samples (approximately 2 mL of whole blood) for CYP2C19 genotype testing shall be collected according to the clinical research schedule ([redacted]). CYP2C19 genotype testing shall be performed at the laboratory test measurement institution (refer to the attached sheet).

9.1.13 Endoscopy (esophagus)

The investigator or sub-investigator shall perform endoscopy according to the clinical research schedule ([redacted]). The investigator or sub-investigator shall take pictures in accordance with a procedure manual (refer to the attached sheet) so that the LA

Classification grade can be determined.
For each research subject, preferably the same person shall perform endoscopy. Prior to endoscopy, the origin of previous pictures shall be located, and preferably the adjacent areas shall be photographed.

Research subjects shall visit the study site for endoscopy under fasted conditions.

The investigator or sub-investigator shall classify the grade of EE in accordance with Table 9.b, "Classification of EE severity", which defines Grade O as "no mucosal break," in addition to the Los Angeles Classification (LA classification). [7)]

The investigator or sub-investigator shall record Barrett mucosa at endoscopy according to the following classification:
•Yes (≥ 3 cm), yes (< 3 cm), no, unknown
Esophageal hiatal hernia shall be recorded at endoscopy according to the following classification:
•Yes (≥ 2 cm), yes (< 2 cm), no, unknown
The investigator or sub-investigator (with assistance of the research collaborator if necessary) shall store endoscopic pictures taken at each time point in the medical record. In addition, endoscopic results (LA classification, and classification of Barrett mucosa and esophageal hiatal hernia) shall be recorded on electronic media or described in the medical record and stored, as well as be recorded on the CRF. An endoscopy report may be affixed to the medical record, instead of describing the results in the medical record.

Table 9 (b) Classification of EE severity

Grade O	No mucosal break
Grade A	Mucosal break with a diameter of no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B	At least one mucosal break with a diameter of longer than 5 mm that does not extend between the tops of two mucosal folds
Grade C	At least one mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference
Grade D	Mucosal break which involves at least 75% of the circumference

Mucosal break: area with white coating or redness clearly demarcated from the adjacent normal mucosa

Definition of "healed"

A research subject who has no endoscopic mucosal break (assessed as Grade O according to the classification of EE severity) during the healing phase shall be considered healed.

Definition of "recurred"

A research subject who has endoscopically confirmed EE of LA Classification Grades A to D during the maintenance phase shall be considered recurred.

9.1.14 Endoscopy (stomach)

The investigator or sub-investigator shall perform endoscopy according to the clinical research schedule ([redacted]). The investigator or sub-investigator shall take pictures in accordance with a procedure manual (refer to the attached sheet) so that endoscopic findings can be determined. At endoscopy at the start of the healing phase, as many areas of the stomach as possible shall be photographed to understand the pre-study conditions.
For each research subject, preferably the same person shall perform endoscopy. Prior to endoscopy, the origin of previous pictures shall be located, and preferably the adjacent areas shall be photographed.

The investigator or sub-investigator shall classify endoscopic findings into the presence or absence of fundic gland polyp, hyperplastic polyp, cobblestone mucosa, multiple white flat elevation, and black spots, as well as other findings.

Research subjects shall visit the study site for endoscopy under fasted conditions.

Endoscopic results (presence or absence of fundic gland polyp, hyperplastic polyp, cobblestone mucosa, multiple white flat elevation, and black spots, as well as other findings) obtained at each time point shall be recorded on electronic media or described in the medical record and stored, as well as be recorded on the CRF by the investigator or sub-investigator (with assistance of the research collaborator if necessary). An endoscopy report may be affixed to the medical record, instead of describing the results in the medical record.

9.1.15 Gastric mucosa histopathology

Gastric mucosa shall be sampled according to the clinical research schedule ([redacted]) to evaluate the effect of the study drug on gastric mucosa of the middle gastric body and around the pyloric region (refer to the attached sheet).

Gastric mucosa histopathology shall be performed by the person responsible for gastric mucosa evaluation using gastric mucosa specimens prepared by the pathological specimen preparation facility (refer to the attached sheet).

Observation and evaluation items are as follows:

[Observation and evaluation items]

1) Greater curvature of the middle gastric body

Presence or absence of malignant alteration of epithelial cells [no] [yes] [unevaluable]

Presence or absence of prominence/hyperplasia of wall cells [no] [yes] [unevaluable]

Presence or absence of hyperplasia of crypt epithelial cells [no] [yes] [unevaluable]

Presence or absence of proliferation of endocrine cells [no] [yes*: 1, 2, 3, 4] [unevaluable]

2) Greater curvature of the antrum within 2 cm from the pylorus

Presence or absence of hyperplasia of G cells [no] [yes] [unevaluable]

*Classification of proliferation pattern of endocrine cells:

1=atrophic ECM (endocrine cell micronest), 2=hyperplastic ECM,

3=neoplastic ECM, 4=typical carcinoid

9.1.16 Histological evaluation of gastritis according to the Sydney classification

Gastric mucosa shall be sampled according to the clinical research schedule ([redacted]) to evaluate gastritis histologically according to the Sydney classification. [8)]

Histological evaluation of gastritis according to the Sydney classification shall be performed by the person responsible for gastric mucosa evaluation using gastric mucosa specimens prepared by the pathological specimen preparation facility (refer to the attached sheet).

Observation and evaluation items are as follows:

[Observation and evaluation items]

1) Greater curvature of the middle gastric body and greater curvature of the antrum within 2 cm from the pylorus

Inflammation (mononuclear infiltration)	[no] [yes: mild, moderate, severe] [unevaluable]
Activity (neutrophilic infiltration)	[no] [yes: mild, moderate, severe] [unevaluable]
Atrophy	[no] [yes: mild, moderate, severe] [unevaluable]
Intestinal metaplasia	[no] [yes: mild, moderate, severe] [unevaluable]
H. pylori	[no] [yes: mild, moderate, severe] [unevaluable]

9.1.17 Pregnancy

If pregnancy of a female research subject is found during her participation in this clinical research, with agreement of the female research subject, the principal investigator or investigator shall inform the research subject's obstetrics gynecology physician about the fact of her participation in the clinical research and details of the study drug or control drug at the onset of the pregnancy.

All reported pregnancies shall be followed up to final outcome, using the pregnancy form by the investigator or sub-investigator. The outcome, including any premature termination, shall be reported to Takeda. Evaluation after delivery shall also be conducted.

9.1.18 Record of research subjects who are withdrawn before randomization

A CRF shall be created for all research subjects who sign the consent form and are then withdrawn before randomization (before the start of the healing phase).

The following items are to be recorded on the CRF:

- Date of consent obtainment
- Date of birth

- Sex
- Eligibility
- Reason for discontinuation

The primary reason for withdrawal before randomization shall be recorded on the CRF according to the following classification:

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria
- Serious deviation from the protocol
- Lost to follow-up
- Voluntary discontinuation <specify the reason>
- Discontinuation of the entire study
- Others <specify the reason>

Research subject ID codes assigned to research subjects withdrawn from the research before randomization shall not be reused.

9.1.19 Recording of randomization

Research subjects to be randomized shall meet all of the inclusion criteria and shall not meet any of the exclusion criteria according to Section 8.2. The investigator or sub-investigator shall specify the reason why the research subject cannot be randomized.

9.2 Compliance of research subjects

The investigator or sub-investigator shall confirm the compliance with taking study drug or control drug of the research subject at every VISIT.

Furthermore, at each VISIT, the whole drug-administration status shall be classified into 4 categories, as follows: “took the drug properly (≥ 90%),” “usually took the drug (≥ 70%),” “took the drug more than half of the time (≥ 50%),” and “took the drug less than half of the time (< 50%).”

Medication instruction shall be given to research subjects throughout the research period. If poor compliance with study treatment (e.g., < 50% of the prescribed dose) (excluding suspension/interruption) after the previous visit has been found and does not

improve, the research subject may be withdrawn from the research if appropriate for the circumstances.

9.3 Implementation time point of the test and observation items

The schedule for all tests, observations, and evaluations is shown in [redacted]. The investigator or sub-investigator shall perform the tests, observations, and evaluations at the time points shown below.

9.3.1 At the start of the healing phase [VISIT H1 (Week 0 in the healing phase)]

After acquisition of informed consent, a physical examination and tests for enrollment to the research shall be performed. Eligibility of patients shall be determined in accordance with the inclusion and exclusion criteria as described in Section 7.0. After all tests/observations/evaluations at the start of the healing phase (Week 0 in the healing phase) are completed, the registration center shall be informed (access to the web subject registration system), and research subjects shall be randomized at the start of the healing phase (Week 0 in the healing phase) in accordance with Section 8.2.

Refer to Section 9.1.18 for the recording of research subjects who are withdrawn before randomization.

Tests and observations to be performed and endpoints to be assessed at the start of the healing phase (Week 0 in the healing phase) are shown below.

- Informed consent procedure
- Demographic data, medical history, previous treatment drug(s)
- Physical examination
- Vital signs
- Height, weight, and BMI
- Concomitant drug(s)
- Concurrent diseases
- Laboratory tests
- Serum gastrin
- Serum pepsinogen I/II, serum chromogranin A

- *H. pylori* urea breath test
  (In principle, the urea breath test shall be performed after endoscopy at the start of the healing phase.)
- CYP2C19 genotype testing
  (In principle, the genotype testing shall be performed at the start of the healing phase. It may be performed between the start and end (or discontinuation) of the healing phase.)
- Endoscopy
- Gastric mucosa histopathology
- Histological evaluation of gastritis
- Compliance status

9.3.2 At the end of the healing phase [VISIT H2 (Week 4 in the healing phase)]

Tests and observations to be performed and endpoints to be assessed at the end of the healing phase (Week 4 in the healing phase) are shown below. For research subjects with no endoscopic healing of EE at Week 4 in the healing phase, the tests/observations/evaluations shall be performed at Week 8 in the healing phase (VISIT H3), when the healing phase shall conclude.

- Physical examination
- Vital signs
- Concomitant drug(s)
- Laboratory tests
- Serum gastrin
- Serum pepsinogen I/II, serum chromogranin A
- Endoscopy
- Compliance status
- Adverse events

9.3.3 At the end or discontinuation of the healing phase [VISIT H3 (Week 8 in the healing phase)]

For research subjects with no endoscopic healing of EE at Week 4 in the healing phase who enter Week 8 in the healing phase (VISIT H3), which is the end of the healing phase, tests and observations to be performed and endpoints to be assessed are shown below.

Research subjects with no endoscopic healing of EE at the end of the healing phase (Week 8 in the healing phase) shall complete the study.

For research subjects who are withdrawn from the research during the healing phase, efforts shall be made to perform all tests/observations/evaluations scheduled at the end of the healing phase. Endoscopy is not mandatory.

- Physical examination
- Vital signs
- Concomitant drug(s)
- Laboratory tests
- Serum gastrin
- Serum pepsinogen I/II, serum chromogranin A
- Endoscopy
- Compliance status
- Adverse events

9.3.4 At the start of the maintenance phase [VISIT M1 (Week 0 in the maintenance phase)]

A physical examination for entry to the maintenance phase shall be performed after the end of the healing phase. Eligibility of research subjects shall be determined in accordance with the inclusion and exclusion criteria as described in Section 7.0.
Research subjects shall receive the study drug or control drug for the maintenance phase after the completion of all tests/observations/evaluations at the end of the healing phase (at the start of the maintenance phase).

9.3.5 Weeks 12 (VISIT M2) to 228 (VISIT M15) in the maintenance phase

Tests and observations to be performed and endpoints to be assessed at Weeks 12 to 228 in the maintenance phase are shown below. Those to be performed or assessed only at specified VISITs are indicated as such by specifying the relevant VISITs.

- Physical examination
- Vital signs
- Concomitant drug(s)
- Laboratory tests
- Serum gastrin
- Serum pepsinogen I/II, serum chromogranin A
  [Weeks 24 (VISIT M3), 48 (VISIT M5), 108 (VISIT M10), 156 (VISIT M12), and 204 (VISIT M14) in the maintenance phase]
- Endoscopy
  [Weeks 48 (VISIT M5), 108 (VISIT M10), 156 (VISIT M12), and 204 (VISIT M14) in the maintenance phase]
- Gastric mucosa histopathology
  [Weeks 48 (VISIT M5), 108 (VISIT M10), 156 (VISIT M12), and 204 (VISIT M14) in the maintenance phase]
- Histological evaluation of gastritis
  [Weeks 48 (VISIT M5), 108 (VISIT M10), 156 (VISIT M12), and 204 (VISIT M14) in the maintenance phase]
- Compliance status
- Adverse events

9.3.6 At the end [VISIT M16 (Week 260 in the maintenance phase)] or discontinuation of the maintenance phase

Week 260 in the maintenance phase shall be the final VISIT (VISIT M16), and the tests, observations, and evaluations listed below shall be performed. If the study is discontinued, the same tests, observations, and evaluations as those at the end of the maintenance phase shall be performed.

- Physical examination
- Vital signs

- Concomitant drug(s)
- Laboratory tests
- Serum gastrin
- Serum pepsinogen I/II, serum chromogranin A
- Endoscopy
- Gastric mucosa histopathology
- Histological evaluation of gastritis
- Compliance status
- Adverse events

At completion of the clinical research, the status of all research subjects administered the study drug or control drug shall be recorded on the CRF.

10.0 Adverse events

10.1 Definitions

10.1.1 Adverse events and disease or the like

An adverse event is defined as any untoward medical occurrence in a patient or a research subject receiving a pharmaceutical product (including the study drug or control drug). It does not necessarily have an apparent causal relationship with this pharmaceutical product (including the study drug or control drug).

An adverse event can therefore be any unfavorable and unintended sign (e.g., a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug or control drug), regardless of whether it is considered related to the pharmaceutical product (including the study drug or control drug).

"Disease or the like" is defined as disease, disability, death, or infection that is suspected of being due to the conduct of a specified clinical research including any unintended sign, clinically significant laboratory change, symptom and aggravation of a concurrent disease.

An adverse event that was considered causally related to the study drug or control drug, or research-specific procedures by the investigator or sub-investigator shall be regarded as "disease or the like."

10.1.2 Considerations for adverse events

Generally unfavorable findings are described below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of an existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation or a change in the dose of the study drug, control drug, or concomitant medications
- Considered unfavorable by the investigator or sub-investigator

Diagnosis name and signs/symptoms:

Adverse events shall be recorded by diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms shall not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, the signs or symptoms shall be recorded as the adverse event.

Laboratory test values and ECG findings:

Abnormal laboratory values and ECG findings shall be recorded as adverse events when the investigator or sub-investigator judges the results are clinically problematic (in other words, when certain action or medical practice is required, or when the investigator or sub-investigator judges the change has exceeded the normal physiological variation range of the research subject). Retest and/or continued monitoring of an abnormality are not considered medical practice. Also, repeated or additional conduction of non-invasive tests for verification, evaluation, and monitoring of an abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of a disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the adverse event shall be handled by its diagnosis name.

Pre-existing conditions at the start of the healing phase: A disease or symptom that had been present since before the start of the healing phase shall be regarded as a concurrent disease and not an adverse event. When a concurrent medical condition is aggravated, the aggravation shall be determined as an adverse event and the investigator or sub-investigator shall record on the CRF that the adverse event is an aggravation of the concurrent disease (e.g., “aggravation of hypertension,” etc.).

If a research subject has a pre-existing episodic condition (e.g., asthma, epilepsy), each episode shall be recorded as an adverse event if the episodes become more frequent, serious, or severe in nature. If a research subject has a chronic concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition shall be recorded as adverse event if the degree of the worsening exceeds that which would be expected. The investigator or sub-investigator shall ensure that the adverse event term to be recorded represents the change in the condition from baseline (e.g. “worsening of…”).

Worsening of adverse events:
If a research subject experiences a worsening of the adverse event after a change in the dose of the study drug or control drug, or secondary signs and symptoms are caused by the adverse event, the worsening or the secondary signs and symptoms shall be recorded

as a new adverse event on the CRF. The investigator or sub-investigator shall use an adverse event term that explicitly means a change of the condition (e.g., "worsening of…").

Change of severity of adverse events:
If the research subject experiences changes in the severity of an adverse event, the event shall be recorded once, at its peak severity.

Previously planned surgery or treatment:
Preplanned surgeries or interventions that were scheduled before the start of the healing phase shall not be considered adverse events. However, when the existing symptom is aggravated to a degree requiring emergency surgery or treatment, the condition or the event shall be considered an adverse event. A concurrent disease that resulted from previously planned surgery shall be reported as an adverse event.

Non-urgent surgery or treatment:
Non-urgent surgery or treatment that does not induce a change in the condition of a research subject (cosmetic surgery, etc.) shall not be considered an adverse event; however, it shall be recorded in the source documents. Concurrent diseases due to a non-urgent surgery shall be reported as an adverse event.

Insufficient clinical response (lack of efficacy):
Insufficient clinical response, efficacy, or pharmacological action shall not be recorded as an adverse event. The investigator or sub-investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

Overdose of the study drug or control drug
Overdose of the study drug without manifested symptoms shall not be recorded as an adverse event, but the overdose shall be recorded on the "Overdose" page of the CRF. Any manifested symptoms shall also be recorded as adverse events on the "Adverse events" of the CRF.

Serum gastrin level, pepsinogen I/II levels:
An increase in serum gastrin level, pepsinogen I level, or pepsinogen II level, which is due to the pharmacological action of the study drug or control drug, shall not be recorded as an adverse event. However, an increase in serum gastrin level leading to withdrawal of the research subject from the study shall be reported as an adverse event.

10.1.3 Serious adverse events

Of all the unfavorable medical events that develop with administration of drugs (including the study drug or control drug, irrespective of dose), a serious adverse event is an event that:

1. results in death,
2. is life threatening*,
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. leads to a congenital anomaly/birth defect,
6. other medically significant condition: a medically important event that causes a risk to a research subject even if it is not immediately life-threatening and does not result in death or hospitalization, or requires an action or treatment to prevent the results described in 1 to 5 above. In addition, points described in the Takeda Medically Significant Adverse Event List (Table 10 (a)) are included in this section.

* The term "life threatening" refers to an event in which the research subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10 (a) Takeda Medically Significant Adverse Event List

Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsades de pointes/ ventricular fibrillation/ventricular tachycardia	Acute hepatic failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/ Oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome/ malignant hyperpyrexia
	Spontaneous abortion/ stillbirth and fetal death
	Confirmed or suspected transmission of infection by a medicinal product
	Confirmed or suspected endotoxin shock

10.1.4 Severity of adverse events

The severity of adverse events shall be classified and defined as shown below.

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities.

10.1.5 Causality of adverse events

The causal relationship of each adverse event to the study drug or control drug shall be classified and defined as shown below.

Related	An adverse event that follows an apparent temporal sequence (including clinical course after discontinuation). Possibly due to the study drug or control drug, although other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment are also suspected.
Not related	An adverse event that does not follow an apparent temporal sequence from administration of the study drug and control drug. Very likely due to other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment.

10.1.6 Relationship to study procedures

The relationship shall be recorded as "Yes" if the investigator or sub-investigator considers that there is reasonable possibility that an adverse event is due to a study procedure. Otherwise, the relationship shall be recorded as "No."

10.1.7 Date of onset

The date of onset of adverse events shall be determined according to the following rules:

Adverse event	Date of onset
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the research subject and/or the investigator or sub-investigator.
Asymptomatic diseases	The date on which a diagnosis was confirmed through a test(s). The date on which a diagnosis was confirmed, even when the test results indicate an old sign(s) of the disease or an approximate time of its onset.
Exacerbation of concurrent diseases	The date on which the first worsening of diseases/symptoms was noted by the research subject and/or the investigator or sub-investigator.
Onset of a test abnormality after the start of the healing phase	The date on which a clinically significant laboratory abnormality was detected.
Worsening of a baseline test abnormality after the start of the healing phase	The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter.

10.1.8 Date of resolution

The date of resolution of an adverse event is the date on which the research subject recovered (including resolution with sequelae). If a research subject died due to the adverse event concerned, it shall be the date of death. The adverse event shall be recorded as “ongoing” if the research subject has not yet recovered by the end of the study.

10.1.9 Actions taken for the study drug or control drug

Actions taken for the study drug or control drug shall be classified or defined as shown below.

Drug withdrawn	The study drug or control drug is discontinued because of an adverse event (including withdrawal by the research subject at his/her discretion). If the study drug or control drug is continued after the study termination, the action should be "Dose not changed".
Dose not changed	The dose was not changed after the onset of the adverse event. The study drug or control drug was discontinued, reduced, or increased because of another adverse event. The study drug was discontinued or reduced for a reason other than the adverse event, e.g., inadvertence of the research subject.
Unknown	It has not been possible to determine what action has been taken because the research subject is lost to follow-up.
Not Applicable	The administration of the study drug or control drug had already been completed or discontinued before the onset of the adverse event.
Dose reduced	The dose of the study drug or control drug was reduced because of the adverse event (including dose reduction by the research subject at his/her discretion).
Dose increased	The dose of the study drug or control drug was increased because of the adverse event (including dose increase by the research subject at his/her discretion).
Washout	The study drug or control drug was suspended (i.e., interrupted) because of the adverse event (including suspension/interruption by the research subject at his/her discretion), but resumed later.

10.1.10 Outcome

Outcome of adverse events is classified as follows:

Category	Criteria
Recovered	Disappearance or recovery of symptoms and findings Laboratory values returned to normal or baseline
Improved	The intensity is lowered by one or more stages Symptoms or findings mostly disappeared Laboratory values improved, but have not returned to normal or baseline The research subject died from a cause other than the concerned adverse event while the condition was resolving (recording of the date of death unnecessary)
Not recovered	No change in symptoms, findings, or laboratory data The symptoms, findings, or laboratory data on the final day of observable period were aggravated compared with the date of onset Irreversible congenital anomaly The research subject died from another cause before resolution of the concerned adverse event (recording of the date of death unnecessary)
Recovered with sequelae	Disability that disturbs daily life
Death	Direct relationship between death and the concerned adverse event "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same research subject is not considered as death. The date of death shall be recorded.
Unknown	Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

*10.2.1.1 **Adverse event collection period***

Collection of adverse events shall commence at the start of the healing phase (VISIT H1) and continue until the end of the maintenance phase (VISIT M23).

*10.2.1.2 **Collection, evaluation, and reporting of adverse events***

At each study visit, the investigator or sub-investigator shall check for the presence of any onset of subjective symptoms. A neutral question, such as "How have you been feeling since your last visit?" may be asked to collect any adverse events that occurred between the previous and present visits.

At each study visit, the investigator or sub-investigator shall pay attention to presence of diarrhea, gastrointestinal infections, bone fracture and pneumonia. The principal investigator or investigator shall conduct an examination and follow up on any relevant information as possible, if the onset of subjective symptoms will be suspected.

The investigator or sub-investigator shall follow up all research subjects experiencing an adverse event irrespective of the causal relationship with the study drug or control drug, until the symptom has resolved, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent and irreversible adverse events). All adverse events shall be entered on the CRF, with the event term, onset date, resolution date, onset time, severity, causal relationship with the study drug or control drug (i.e. "Unrelated" or "Related"), action taken for the study drug or control drug, outcome, causal relationship with any study procedure (with specific procedure if assessed to be causally related), and seriousness.

In addition, the investigator shall report an adverse event in accordance with a procedure manual prepared separately, depending on assessment results of its seriousness and causal relationship with the study drug or control drug (whether it was assessed as "serious" and "disease or the like").

Follow-up period of adverse events shall be until recovery of the adverse events, or the time when the investigator or sub-investigator judges that further follow-up would be unnecessary.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it shall be reported according to the following procedures.

At the time of onset of a serious adverse event or notification of the onset by the research subject, etc., the investigator shall report the serious adverse event to the contract research organization (CRO) to whom Takeda has entrusted responsibility (for the contact information, refer to the attachment) immediately (within 1 working day of becoming aware of the event onset) regardless of whether it is considered causally related to the study drug or control drug. Furthermore, the investigator shall submit the detailed report using the pre-defined form through CRO within 8 working days to the representative investigator if the event was assessed as "serious" and "disease or the like" and within 10 calendar days to Takeda unless the event was assessed as "serious" and not "disease or the like." The details shall be reported in accordance with a procedure manual prepared separately.

Furthermore, it shall be mandatory to include the contents below in the report to be submitted to Takeda within 1 working day, and other items shall be reported as far as possible.

- Brief description of adverse event and the reason for why it was determined as serious
- Clinical research title
- Research subject ID codes
- Name of study site
- Name of the investigator or sub-investigator
- Name of the study drug or control drug
- Determined causal relationship

The investigator or sub-investigator shall report spontaneously reported serious adverse events that are collected even after the adverse event collection period to Takeda.

10.2.3 Reporting of additional information concerning adverse events

If Takeda requests provision of additional information concerning adverse events for reporting to regulatory authorities, the investigator or sub-investigator shall confirm the necessary additional information and enter in the electronic data capture (EDC) system or submit a report within the period specified by Takeda.

10.3 Follow-up of serious adverse events

When information that was not included in the detailed report was obtained later, the investigator or sub-investigator shall state it in the copy of the report on serious adverse events, or create another document and submit it to the contact address shown on the attached sheet. Relevant data collected at the study site (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the representative investigator, Takeda, or the certified review board upon request.

The investigator or sub-investigator shall follow-up all serious adverse events, etc., until recovery is confirmed, or the final outcome is determined.

10.3.1 Reporting of serious disease or the like to the certified review board and regulatory authorities

When the representative investigator receives a report of a serious disease or the like from the investigator, he/she shall consult the certified review board, and submit this information to investigators at study sites that are conducting this clinical research through the CRO consigned by Takeda. The investigators shall report the content of such information to the supervisors of the study sites.

Takeda shall report, in accordance with regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the investigators, and the supervisors of the study sites.

From the time point of first acknowledging the event or receiving additional information, Takeda or the CRO consigned by Takeda shall comply with regulatory required time frames for reporting, and make emergency reports concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, Takeda shall, in the same way, make an emergency report of other critical safety information that may have a major effect on the risks/benefits of the study drug or control drug, continuation of study drug or control drug administration, or continuation of clinical research.

11.0 COMMITTEE ESTABLISHED FOR THIS CLINICAL RESEARCH

11.1 Research Steering Committee

The Research Steering Committee shall be composed of the chairperson and members of the committee, and Takeda. The Research Steering Committee shall supervise implementation and reporting of the clinical research, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the protocol appropriately. The responsibilities of the committee shall be prescribed in the procedures of the Research Steering Committee.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

The CRO to whom Takeda has entrusted responsibility shall be in charge of implementing data management operation according to the standard operating procedures, independently from Japan Medical Office of Takeda. Adverse events, medical history, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the World Health Organization (WHO) Drug Dictionary.

12.1 Case report form

The investigator or sub-investigator shall complete a CRF for each research subject who has signed the informed consent form.

Takeda or its designee shall provide the study sites with access authorization to the EDC system. Before use of the EDC system, the CRO to whom Takeda has entrusted responsibility shall provide training to the investigator, sub-investigators, and study collaborators. The CRF shall be used to report the information collected during the research period to Takeda. The CRF shall be prepared in Japanese. Data shall be directly entered in preparing the CRF.

A change or correction of the CRF shall be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The investigator shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the CRF. The investigator bear full responsibility for the accuracy and reliability of all the data entered on the CRF.

The following data shall be recorded on the CRF directly, except for those recorded in the source documents:

- *H. pylori* urea breath test results
- Severity, degree, the causal relationship with the study drug, control drug, or the study procedures, outcome

The following data shall not be directly recorded on the CRF:

- Laboratory test results
- Measured serum gastrin level
- Measured pepsinogen I/II levels and serum chromogranin A level

When the investigator or sub-investigator makes a change or correction in the data entered on the CRF after fixation of clinical data base, a record (Data Clarification

Form) of change or correction on the CRF provided by the CRO to whom Takeda has entrusted responsibility shall be used. The investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

Takeda or the designee shall confirm that the CRF has been made appropriately in conformity with the procedure defined for each research. Takeda or its designee shall have access to the medical records of the research subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF shall be the property of Takeda, and the investigator or sub-investigator shall not disclose the information to a third party without written permission from Takeda.

12.2 Timing of data entry into the EDC system

Takeda or its designee shall request the investigator or sub-investigator to promptly enter data into the EDC system following enrollment of the research subject, each visit during study treatment, and completion/discontinuation of the study.

1. Start of the healing phase: within 2 weeks (14 days) from the start date of the healing phase
2. During the treatment/maintenance phase: within 2 weeks (14 days) from each VISIT
3. Discontinuation of the treatment/maintenance phase: within 4 weeks (28 days) from the date of discontinuation in the treatment/maintenance phase
4. Gastric mucosa histopathology results: within 2 weeks (14 days) from data obtainment
5. Follow-up period: within 2 weeks (14 days) from request for follow-up
6. Queries for entered data: within 2 weeks (14 days) from issue of a query

12.3 Storage and disposal of specimens, information, etc.

The investigator or the supervisor of the study site shall store human-derived specimens and the following materials (information, etc.), including those specified in Section 12.1 and study-specific documents to be used by the regulatory authority and the representative investigator or its designee for investigation and audit. The documents shall include, but shall not be limited to the materials related to the information used in the study such as the research subject ID number list, research subjects' medical records, clinical research work sheet, original signed and dated informed consent forms, an electronic copy of the EDC system with audit trails, and the drug management records.

The investigator shall appropriately retain the specimens/information related to this study for at least 5 years from the end date of this study . However, when the representative investigator and Takeda require a longer storage period, investigator shall discuss the period and methods of storage with the representative investigator and Takeda. When disposing the specimens, information, etc., the investigator shall dispose them anonymously.

13.0 STATISTICAL ANALYSIS METHODS

13.1 Statistical and analytical plans

The person in charge of analysis shall prepare a statistical analysis plan before the acquisition of the informed consent of the earliest research subject, and issue the first edition. Detailed definition of endpoints and analysis methods should be specified in the SAP to deal with all the purposes of the research.

13.1.1 Analysis set

In this clinical research, 4 types of analysis sets, “Full Analysis Set in the maintenance phase,” “Full Analysis Set in the healing phase,” “Safety Data Analysis Set in the maintenance phase,” and “Safety Data Analysis Set in the healing phase,” shall be established. The “Full Analysis Set in the maintenance phase” is defined as research subjects who are randomized and given at least one dose of the study drug or control drug for the maintenance phase,” and the “Full Analysis Set in the healing phase” is defined as research subjects who are randomized and given at least one dose of the study drug or control drug for the healing phase.” In addition, the “Safety Data Analysis Set in the maintenance phase” is defined as research subjects who are given at least one dose of the study drug or control drug for the maintenance phase,” and the “Safety Data Analysis Set in the healing phase” is defined as research subjects who are given at least one dose of the study drug or control drug for the healing phase.”

13.1.2 Analysis of demographic and other baseline characteristics

For the “Safety Data Analysis Set in the maintenance phase,” major demographic and other baseline characteristics shall be aggregated for each treatment group and all combined groups.

13.1.3 Efficacy analysis

(1) Secondary endpoints and the analytical methods

[Secondary endpoints]

Endoscopic EE recurrence rate
EE healing rate at the end of the healing phase

[Analytical methods]

For the “Full Analysis Set in the maintenance phase”, endoscopic EE recurrence rate at each timepoint as well as point estimate and 2-sided 95% confidence interval shall be

calculated for each treatment group. The research subjects with LA Classification Grades whose data are available at each timepoint shall be included in the analysis set.

For the "Full Analysis Set in the healing phase", EE healing rate at the end of the healing phase as well as point estimate and 2-sided 95% confidence interval shall be calculated for each treatment group.

13.1.4 Safety analysis

The following analyses shall be performed in the "Safety Data Analysis Set in the maintenance phase":

(1) Primary endpoint and analytical methods

[Primary endpoint]

Gastric mucosa histopathology

Presence or absence of malignant alteration of epithelial cells

Presence or absence of prominence/hyperplasia of wall cells

Presence or absence of hyperplasia of crypt epithelial cells

Presence or absence of proliferation of endocrine cells

Presence or absence of hyperplasia of G cells

[Analytical methods]

For each gastric mucosa histopathological endpoint (presence or absence of malignant alteration of epithelial cells, presence or absence of prominence/hyperplasia of wall cells, presence or absence of hyperplasia of crypt epithelial cells, presence or absence of proliferation of endocrine cells, and presence or absence of hyperplasia of G cells), the proportion of research subjects who have the event for assessment in maintenance phase shall be calculated for each treatment group.

(2) Secondary endpoints and analytical methods

[Secondary endpoints]

Incidence of adverse events (TEAEs)

Endoscopic findings

Presence or absence of fundic gland polyp

Presence or absence of hyperplastic polyp

Presence or absence of cobblestone mucosa

Presence or absence of multiple white flat elevation

Presence or absence of black spots

Histological evaluation of gastritis according to the Sydney classification

Inflammation (mononuclear infiltration)

Activity (neutrophilic infiltration)

Atrophy

Intestinal metaplasia

H. pylori

Incidence of gastric polyp

[Analytical methods]

A treatment-emergent AE (TEAE) is defined as any AE occurring after the start of study or control treatment for the healing phase. For TEAEs in the maintenance phase, the analyses listed below shall be performed for each treatment group. TEAEs shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA.

- Aggregation of frequencies of all TEAEs in the maintenance phase
- Aggregation of frequencies of TEAEs related to the study drug or control drug in the maintenance phase
- Aggregation of frequencies of all TEAEs in the maintenance phase by severity
- Aggregation of frequencies of TEAEs related to the study drug or control drug in the maintenance phase by severity
- Aggregation of frequencies of TEAEs leading to discontinuation of study treatment or control treatment in the maintenance phase
- Aggregation of frequencies of serious TEAEs in the maintenance phase
- Aggregation of frequencies of all TEAEs in the maintenance phase by time of onset

- Aggregation of frequencies of TEAEs relating to diarrhea, gastrointestinal infections, bone fracture and pneumonia.

For each endoscopic endpoint (presence or absence of fundic gland polyp, presence or absence of hyperplastic polyp, presence or absence of cobblestone mucosa, presence or absence of multiple white flat elevation, and presence or absence of black spots) and each histological endpoint of gastritis according to the Sydney classification [inflammation (mononuclear infiltration), activity (neutrophilic infiltration), atrophy, intestinal metaplasia, and *H. pylori*], the proportion of research subjects who have the event at each time point for assessment shall be calculated for each treatment group.

The incidence of gastric polyp at each point shall be calculated for each treatment group.

13.2 Criteria for interim analysis and premature discontinuation

In addition to the final analysis using data up to the final VISIT, interim analysis using data up to the pre-defined VISIT will be performed once a year during the maintenance phase to evaluate the effect of long term administration of vonoprazan on gastric mucosal tissue as maintenance treatment in patients with recurrent/reactivated erosive esophagitis when data up to the pre-defined VISIT (Week 48 [VISIT M5], Week 108 [VISIT M10], Week 156 [VIST M12], and Week 204 [VIST M14] in the maintenance phase) is collected from all the subjects. The interim analysis is not intended to use decision whether to continue or terminate this study.

13.3 Determination of the planned number of research subjects

As the number of research subjects for entry to the maintenance phase,

Vonoprazan group	130 subjects
Lansoprazole group	65 subjects

To collect data on the effect of long-term vonoprazan on gastric mucosa as well as additional safety data, a sample size of 130 subjects for entry to the maintenance phase was set for the vonoprazan group in consideration of feasibility, with the 1-year (52-week) dropout rate in a Japanese clinical research of vonoprazan into account. Based on the data from previous clinical studies of vonoprazan, data will be collected from approximately at least 100, 50, and 30 subjects in the first, third, and fifth years in the present study, respectively. Since this study will be conducted on an exploratory basis with lansoprazole as control, a sample size of 65 subjects was set for the lansoprazole group with a vonoprazan/lansoprazole ratio of 2:1.

The sample size was not statistically calculated.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the study site

The entity in charge of monitoring shall perform periodic monitoring of study sites during the research to confirm that the research is conducted in accordance with all specifications in the protocol under the supervision of the representative investigator. In the monitoring, the data recorded on the CRF will be checked by comparing them with those in the source documents. Source documents are the original documents, data and records. The investigator and the supervisor of the study site shall ensure that the entity in charge of monitoring and the certified review board have access to the source documents.

The entity in charge of monitoring shall access the records, including the list of research subject ID codes, medical records of the research subjects, and signed and dated original consent forms, to confirm that the research is appropriately conducted in compliance with the protocol. Also, confirm the consistency between CRF and the related source documents. The investigator, sub-investigator, and other personnel involved in the research shall spare sufficient time to facilitate monitoring procedures during visits to the study site.

Detailed procedures for monitoring shall be described in a procedure manual prepared separately.

14.2 Non-compliance with the Clinical Trials Act and the protocol

The investigator or sub-investigator shall record all deviations and non-adherences (hereinafter referred to as “non-compliance”) from the Clinical Trials Act, ICH-GCP or the protocol.

If any non-compliance is found, the investigator shall promptly report the supervisor of the study site and the representative investigator. The representative investigator who received the reporting shall provide such information to investigators in all the study sites.

If any significant non-compliance is found, the representative investigator shall hear opinions of the certified review board, take preventive measures for recurrence, give notice thereof to investigators, sub-investigators, and persons who are engaged in this clinical research at all the study sites to surely prevent the recurrence.

A significant non-compliance is defined as a non-compliance that affects human rights or the safety of research subjects, the progress of the research, or the reliability of

research results. In this clinical research, the following cases are applicable, provided that any protocol deviations to avoid an urgent risk for research subjects or for any other medically unavoidable reasons are excluded.

1. Serious deviations in the course of the conduct of the research (deviation from the inclusion/exclusion criteria, deviation from the termination/discontinuation criteria, deviation from the prescription of study drug or control drug, and deviation from prohibited concomitant medications)
2. Serious non-adherences to applicable laws and regulations (non-adherence to informed consent, non-adherence to the contract, non-adherence to deliberations at the certified review board, and others)

Furthermore, the investigator shall ask the representative investigator, the person who directs the research, and Takeda to discuss whether to revise the protocol as needed. For the revision of protocol, the procedure described in "6.4 Procedures for protocol revision" shall be followed.

14.3 Quality assurance audits and regulatory agency inspections

The study site may be subject to audits by the representative investigator, the CRO to whom Takeda has entrusted responsibility, and the certified review board under the supervision of the representative investigator as needed. In such a case, the auditor of the CRO, etc. shall contact the study site in advance to determine the date of audit. The auditor may ask to visit the facilities where laboratory specimens are collected and any other facilities used during the research. In addition, this research may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the study site is contacted for an inspection by a regulatory body, the representative investigator and Takeda should be notified promptly. The investigator and the supervisor of the study site shall ensure that the auditor has access to all the research-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL RESEARCH

This research shall be conducted with the highest respect for the individual participants (i.e., research subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the Clinical Trials Act, and ICH-GCP. The representative investigator and investigators will conduct the study according to regulatory requirements and in accordance with "Responsibilities of Representative Investigator and Investigators" in [redacted].

15.1 Approval of the Certified Review Board

The approval of the certified review board and the permission of the supervisor of each study site shall be obtained for conducting this clinical research in accordance with the protocol and relevant procedure manuals, etc.

The representative investigator and investigators shall observe all requirements that the certified review board prescribes. The requirements may include notifications to the certified review board, for example, change notification for revision of the protocol, and submission of reports on "disease or the like" in accordance with the Clinical Trials Act, periodic reports, reports on serious non-compliance, and the study completion report. The representative investigator or its designee shall obtain written approval from the certified review board and all relevant documents concerning the above mentioned items.

15.2 Conflict of interests

This clinical research shall be conducted with the support of Takeda.

Prior to the conduction of this clinical research, the representative investigator and investigator shall ensure appropriate management of any conflicts in the conduct of the research(conflict of interest; hereinafter referred to as "COI") of investigators and sub-investigators involved in this clinical research in accordance with the COI management criteria and the COI management plan.

Among the representative investigator, investigators, and sub-investigators, there are some persons who have received personal advantages that meet the COI management criteria from the pharmaceutical company marketing the study drug used in this research, therefore, the summary of COI will be disclosed when publishing research results.

15.3 Informed consent and information sheet, and the agreement of the research subjects

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guidelines on Biomedical Research Involving Human Subjects and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of research subjects in this clinical research (both in and outside Japan: supply to a third party), and disclosure. The informed consent form and the information sheet will explain in detail the nature of the research, its objectives, and potential risks and benefits. The informed consent form will detail the following, in principle, including the requirements of the participant and the fact that research subject is free to withdraw at any time without giving a reason and without any negative effect on the further medical care.

1. The study title and the conduct of this study have been approved by the chief executive of the research implementing entity.
2. The name of the research implementing entity and the name of the principal investigator. (If a collaborative study, the name of the collaborative research implementing entity and the name of the principal investigator from the collaborative research implementing entity should be included.)
3. The study objectives and the significance
4. The study methods (including the purposes of use of specimens and information collected from a research subject) and the duration of the study
5. Reasons for being selected as a research subject
6. Costs that a research subject may need to bear and anticipated risks and benefits
7. A research subject can withdraw his/her consent to participating or staying in the study at any time. (If there is a difficulty in taking actions for the withdrawal as requested by a research subject, etc., this should be indicated with the reason,)
8. A research subject, etc. will not experience any disadvantage even if he/she refuses to participate or continue to be in the study or withdraws the consent.
9. Study information disclosure method
10. A research subject can obtain or have free access to the study protocol and other documents regarding study methods as per request, as far as personal information of other research subjects, etc. are protected and originality of this research is ensured. Also, describe the method to obtain or request access to the information.

11. Handling of personal information, etc. (including the method of anonymization, if applicable)
12. Storage and disposal of specimens and information
13. Research-related conflict of interests of the research implementing entity such as resources for research funding, and that of investigators, etc. such as personal financial profit, etc.
14. Consultation windows for research subjects or persons related to the research
15. Financial burden or reward to research subjects, if applicable, including the details.
16. If the study includes procedures that are not undertaken in regular clinical practice, information on the other treatment options should be provided.
17. If the study includes procedures that are not undertaken in regular clinical practice, treatment the research subjects will be able to receive after study completion should be indicated.
18. Handling of the study results (including accidental findings) related to a research subject, if a significant finding that may affect the research subject's health or genetic characteristics of the offspring may be obtained from the study.
19. If the study includes invasive procedures, indicate whether the health injury caused by participating in this study will be compensated or not, and the contents of the compensation, if applied.
20. If specimens and information obtained from a research subject may be used for a future research unspecified at the time of consent submission or be provided to other research institutions, this should be indicated with the contents of the research assumed at the time of consent.
21. If the study includes invasive procedures (except for mild invasions) and interventions, monitoring staff, audit staff, and Ethical Review Board have access to specimens and information related to a research subject as necessary, as long as confidentiality of the research subject is retained.

The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and research subject information sheet by the committee such as the IEC. The informed consent form and information sheet must be approved by the committee prior to use.

The informed consent form and information sheet shall be written in language that can be easily understood by the potential research subjects. The principal investigator or

investigator shall be responsible for providing detailed explanation of the informed consent form and information sheet to the potential subjects. Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as the IEC.

The principal investigator or investigator shall ensure that the potential research subjects have (1) an opportunity to inquire about the research and (2) sufficient time to decide on their participation. If a potential research subject decides to participate in the research, then the informed consent form must be signed and dated by the potential research subject prior to entering into the research as a subject. The principal investigator or investigator shall instruct the potential research subject to sign using their legal names, not nicknames, using a blue or black ball point ink pen. Also the principal investigator or investigator shall sign and date the informed consent form prior to entering into the research.

Once signed, the original informed consent form shall be retained by the principal investigator or investigator. The principal investigator or investigator shall record the date that the potential research subject signed the informed consent form in the subject's medical record. A copy of the signed informed consent form shall be given to the research subject.

The principalinvestigator or sub-investigator shall follow the same procedure as for obtaining the initial consent when newly obtaining re-consent from the concerned research subject when the informed consent form is revised. The date of obtaining new consent shall be recorded in the research subject's medical record, and a copy of the revised consent form shall be provided to the research subject.

When revising the informed consent form and research subject information sheet, the revised version shall be used after obtaining approval from the certified review board.

15.4 Personal information of research subjects

The persons who are or were engaged in this clinical research shall affirm the principle of the protection of research subjects' private/personal information. Throughout this study, research subject ID codes shall be used to link the subject's source data to the sponsor's research database and research-related documents. Limited information on research subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of research subjects and confirmation of accuracy of research subject ID code.

For verification of the conduct of the research in compliance with this protocol and the Clinical Trials Act, the representative investigator or investigator shall give a permission that the representative investigator, Takeda's designee, representatives of regulatory authorities, designated auditors, and the certified review board can have direct access to research subjects' original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject's research participation, and autopsy reports. The investigator or sub-investigator shall obtain specific authorization of the research subject as part of the informed consent process for access to research subject's original medical records by the representative investigator, Takeda's designee and representatives of regulatory authorities (see Section 15.3).

When providing a copy of source documents to Takeda, the investigator or sub-investigator shall delete information that may lead to identification of an individual (name and address of research subject, other personal information not recorded on the CRF of the research subject).

15.5 Consultation windows for research subjects or persons related to the research

The investigator shall establish a contact service to respond to inquiries concerning this clinical research from research subjects or concerned people. Details of the contacts for inquiries will be described in the informed consent form.

15.6 Financial burden or reward to research subjects

Of the expenses for this clinical research, Takeda shall pay for medical treatment not covered by health insurance and examinations necessary for the research as research expenses. The research subjects shall pay expenses for medical treatment covered by ordinary health insurance.

In addition, the investigator shall pay expenses such as transportation expenses for participation in this clinical research to the research subjects at each visit from the research funds. Details of the financial burden on the research subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and inconveniences to research subjects

15.7.1 Benefits to research subjects

The research subjects will obtain detailed information on the status of his or her EE through participation in this clinical research.

15.7.2 Inconveniences to research subjects

Participation in this clinical research may increase burden on the research subjects due to increased frequencies of visits and examinations, as compared with routine medical practice.

The examinations, observations, and assessments will be performed in accordance with the Schedule of Research Procedures ([redacted]).

15.8 Attribution of research results and access rights

15.8.1 Attribution of research results

All the research specimens, results and data obtained from this research shall belong to Takeda. In addition, secondary use (meta-analysis, etc.) of the specimens and data obtained in this clinical research may be possible by Takeda, the representative investigator, or members of the Research Steering Committee if used in such a way that the specimens and data shall not be linked to personal identification information. The specimens and data can be available for secondary use only when it was collected from research subjects who consented to the participation in this research, using the informed consent form and research subject information sheet in which the possibility of secondary use is clearly described. In addition, necessary measures shall be taken not to identify individuals when publishing research results. When the representative investigator or members of the Research Steering Committee use the specimens and data secondarily, to whom such specimens and data would belong for secondary use onwards will be determined based on discussions with Takeda.

15.8.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by Takeda.

15.9 Reporting of results, Publication, disclosure, and clinical research registration policy

15.9.1 Reporting of results, publication and disclosure

The investigator shall report a written summary of results of the research to the supervisor of the study site and provide Takeda with all the results and data obtained from the research. Only Takeda may disclose the research information to other investigators, sub-investigators or regulatory authorities during the research period, except when required by laws and regulations. Takeda shall be responsible for

publication of the protocol and research-related results (including the public web site) except for other cases permitted in the research contract. The registration of research results to the database introduced and maintained by the Ministry of Health, Labour, and Welfare in accordance with the Clinical Trials Act (Japan Registry of Clinical Trials, hereinafter referred to as "jRCT") shall be performed by the representative investigator or its designee.

During and after the research, Takeda or its designee should promptly summarize the results and present them to medical journals and academic conferences, etc. Takeda may publish any data or information obtained from the research (including data and information provided by the investigator) without obtaining agreement of the investigator.

The investigator or sub-investigator should obtain the prior written approval from Takeda when publishing the information obtained in this research at an academic conference, etc.

Takeda shall report to the supervisor of the study site when final publication of the research results has been made.

15.9.2 Clinical research registration

To ensure that information on clinical research is made accessible to the public in a timely manner and to comply with applicable laws, regulations, and guidelines, Takeda shall register all clinical researches being conducted in patients around the world at public trial registration sites, including at least the website(s) of ClinicalTrials.gov and Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC), before initiation of the clinical research. On such websites, the research location (city, country), subject recruitment status, and contact information for Takeda are open to the public.

The representative investigator or its designee shall register this clinical research to jRCT in accordance with the Clinical Trials Act after obtaining approval from the certified review board.

15.9.3 Clinical trial results disclosure

Takeda shall post the research results, irrespective of the nature of the results, at the public trial registration site(s) of Clinical Trials.gov and JAPIC in accordance with applicable laws and regulations.

The representative investigator or its designee shall register research results to jRCT in accordance with the Clinical Trials Act after reporting it to the certified review board.

15.10 Insurance and compensation for injury

The research subjects participating in this research shall be compensated for any health injury according to local regulations applicable to the study site. Takeda or its designee shall buy an insurance policy to compensate for health injury in research subjects.

Healthy injury in a research subject will be compensated as specified in the study contract. Compensation-related questions by the investigator or sub-investigator should be made to Takeda or its designee.

16.0 REFERENCES

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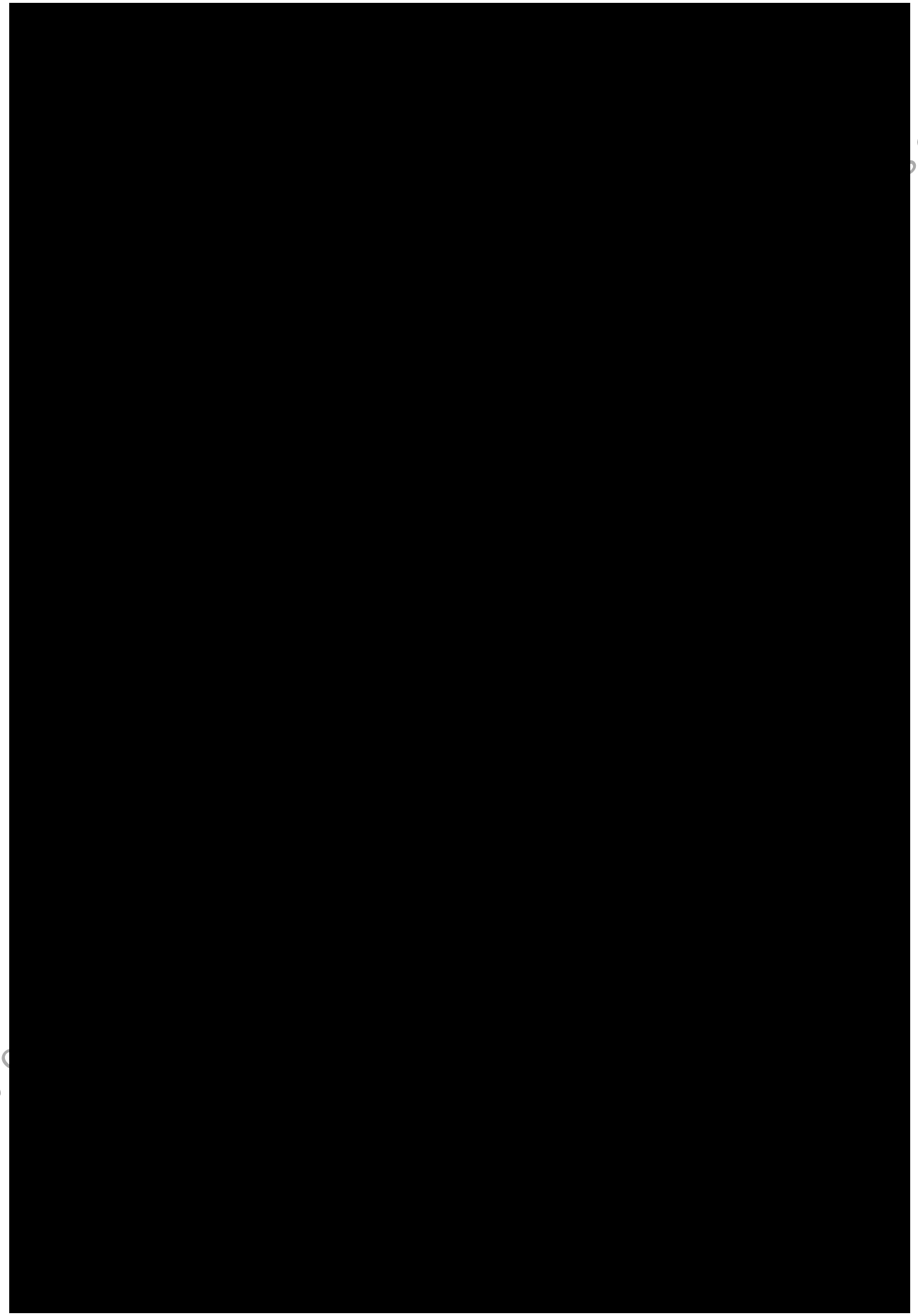

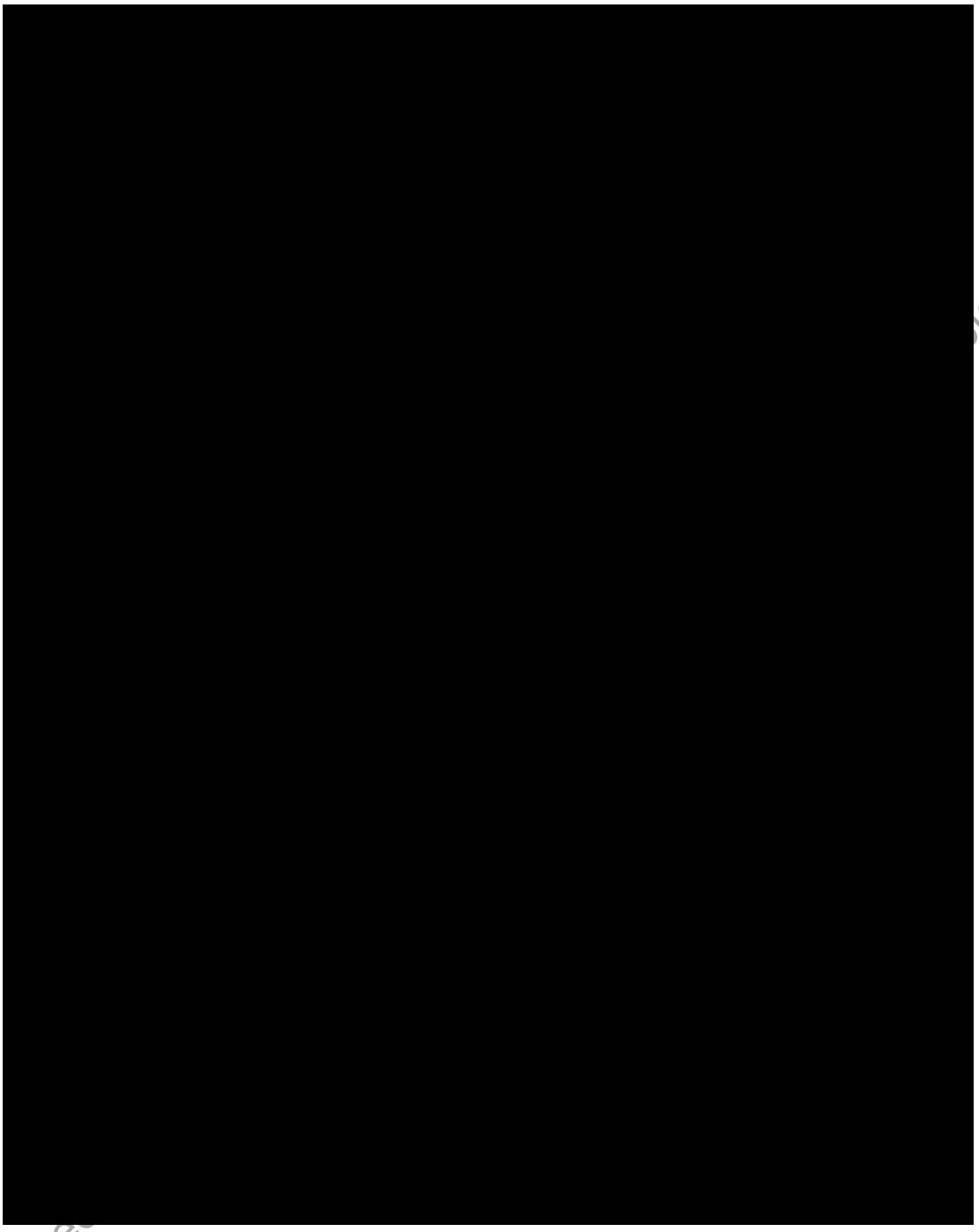

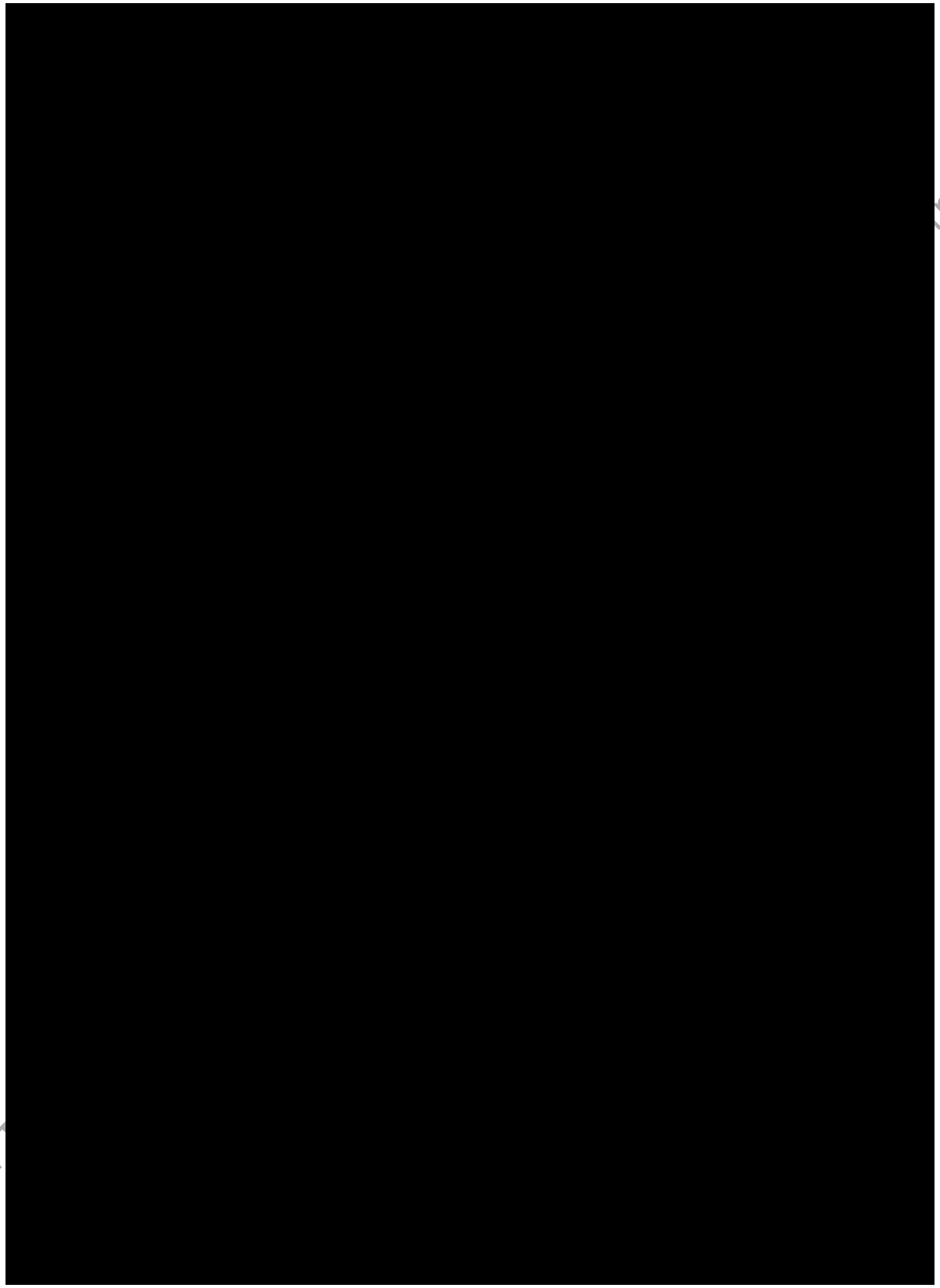

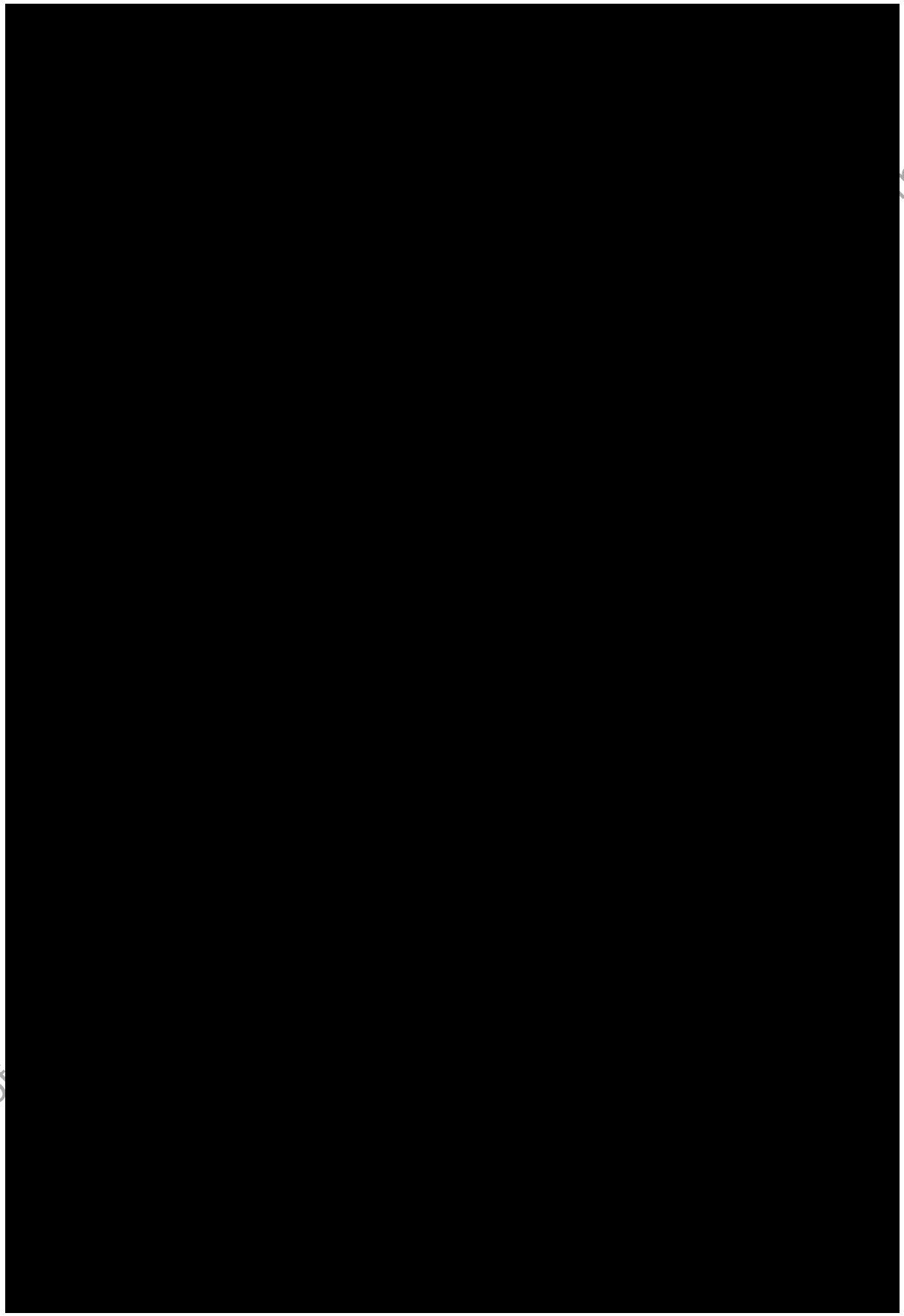

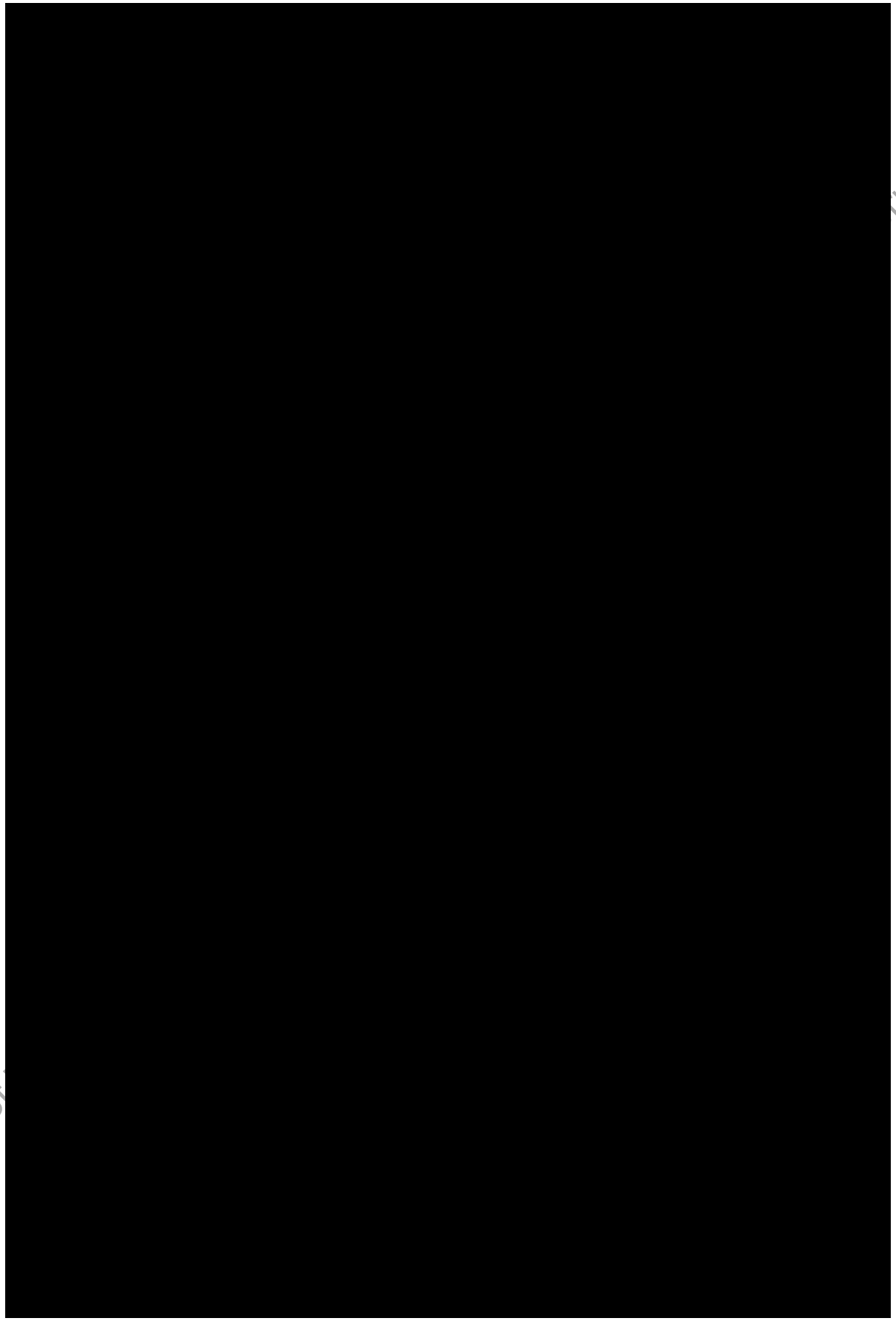

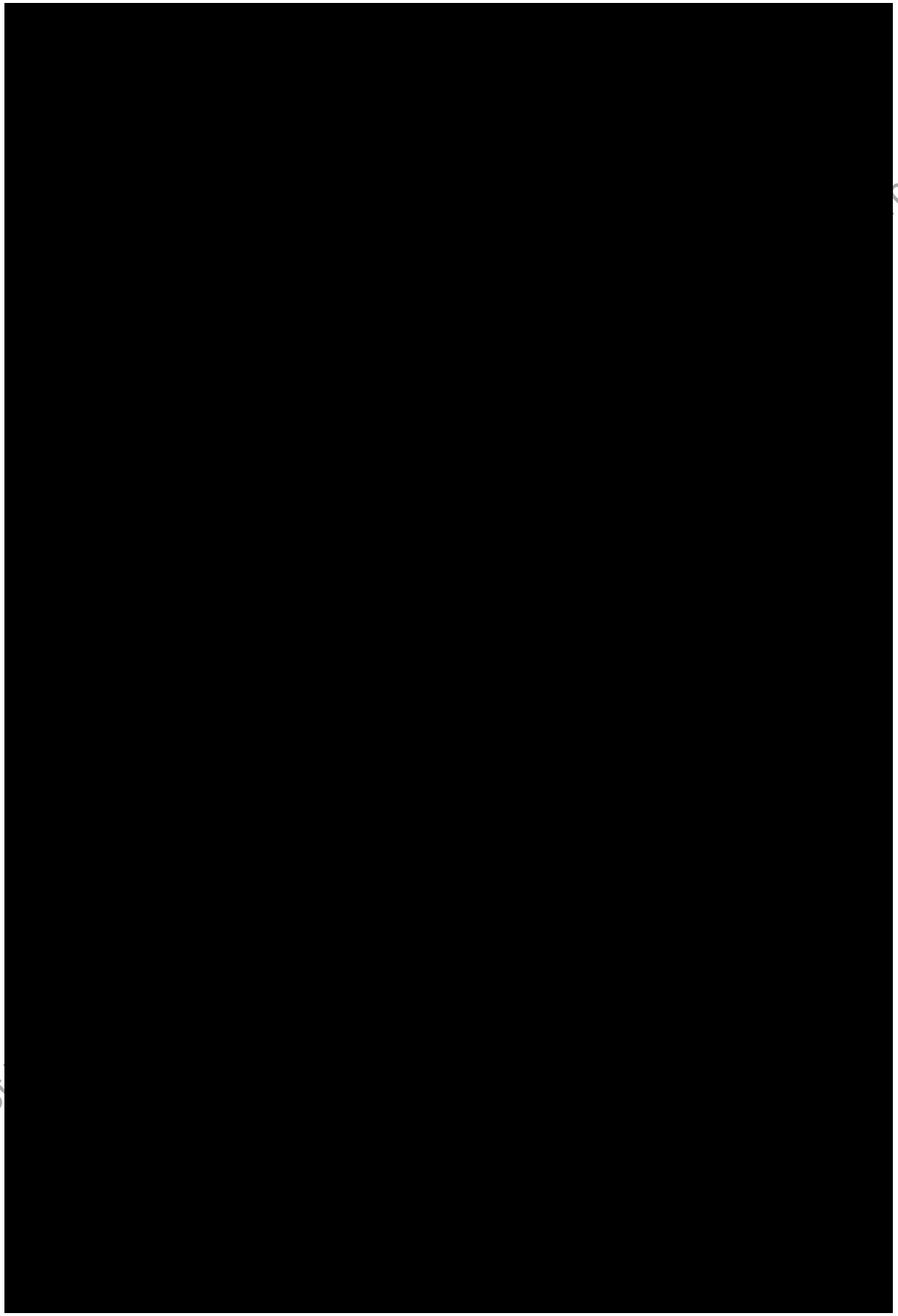

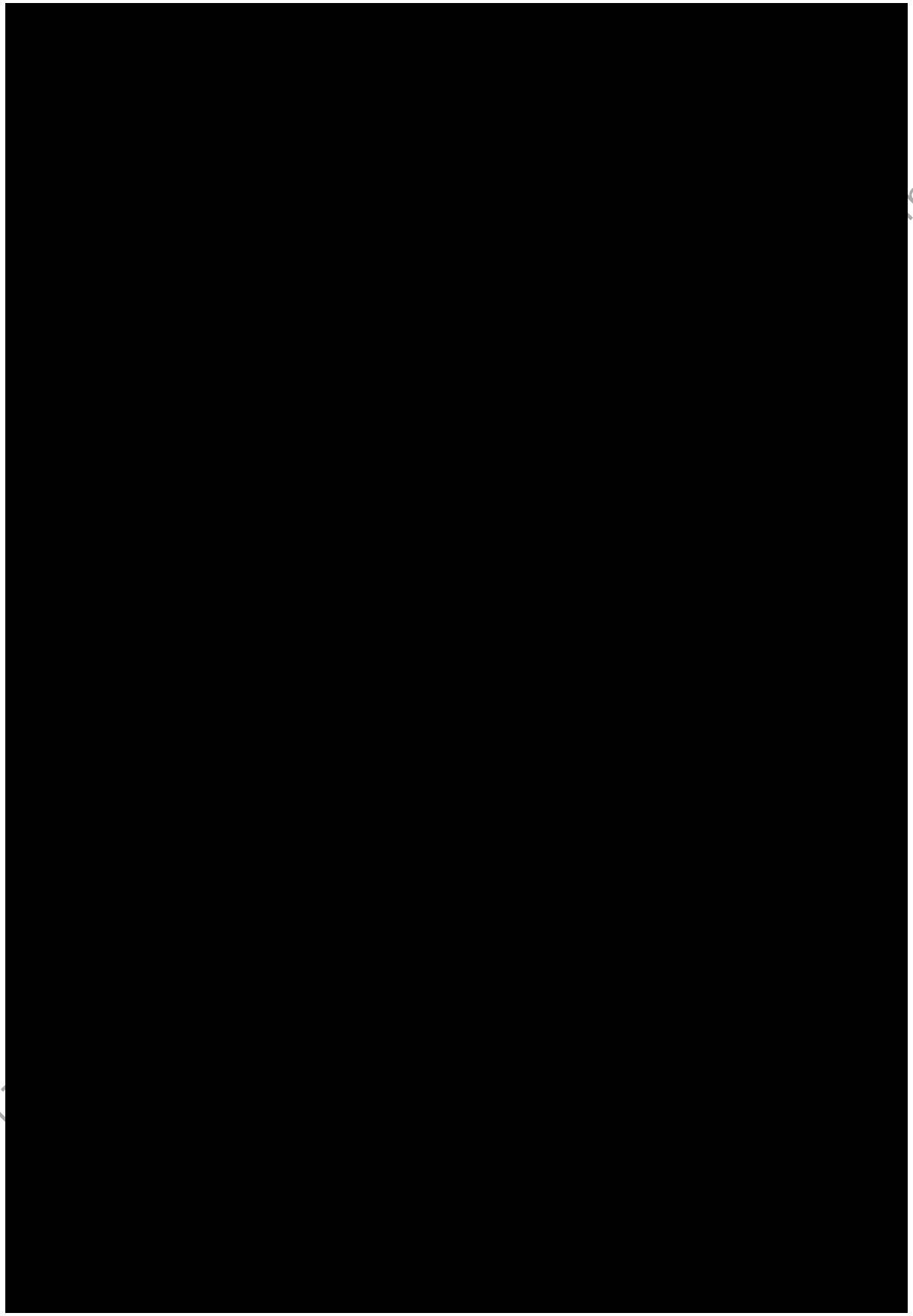

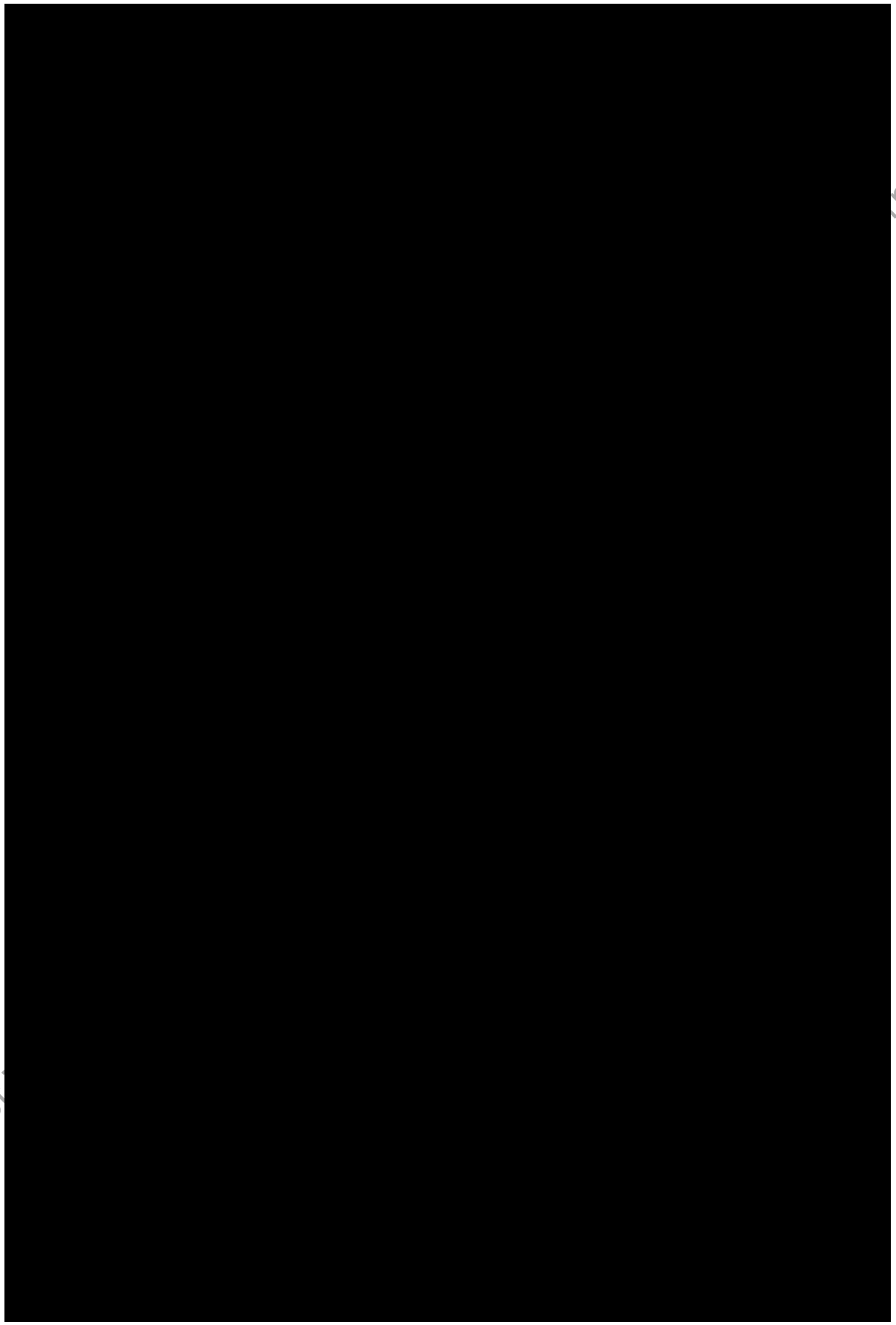

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