Clinical Study Protocol

A Multi-Center, Randomized, Open-Label Study to Evaluate Symptom Relief and Safety after Using Fexuprazan 40 Mg Compared to Esomeprazole 40 Mg in Patients with Gastroesophageal Reflux Disease (GERD).

Protocol No.	**: DW_DWP1401262001**
Version No. (date)	**: 2.1 (19 June 2024)**
Investigational Product	**: Fexuprazan 40mg (Study Drug)** **Esomeprazole 40mg (Control Drug)**
Sponsor	**: Prof. Dr. dr. Ari Fahrial Syam, SpPD, K-GEH, MMB, FACP, FACG, FINASIM**

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[Protocol version history]

No	Version	Version Date	Amendment Summary
1	1.0	2024-01-17	New Version
2	2.0	2024-05-03	- Adding information Daewoong Pharmaceutical Co. Ltd.as collaborative partner - Revision of exclusion criteria - Clarification of study methodology and safety follow-up - Adding the purpose of calculating medication adherence - Adding procedure related to assessment of AE occurs on the subject - Adding Handling and Compensation of Adverse Event - Adding Safety reporting contact of Sponsor - Adding Information of questionnaire validation
3	2.1	2024-06-19	- Correction in Study Schematic figure - Clarify the parties responsible for randomization. - Deletion of stratification separator in randomization method, and adding site number in the randomization number - Revision of statistical analysis from Cochran-Mantel-Haenszel to be Chi SquareTest - Correction in the GERD-Q ,GERD-HRQL and Subject Diary

[Sponsor Acknowledgement]

SPONSOR PROTOCOL SIGNATURE PAGE

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This study has been prepared and reviewed by the Sponsor for distribution to designated clinical sites, associated ethics committees/ institutional review boards, designated contractors, regulatory agencies and with permission by the Sponsor.

The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the guidelines on International Council for Harmonization Good Clinical Practice (ICH-GCP).

Approved by the following:

Prof. dr. Ari Fahrial Syam, SpPD, K-GEH, MMB, FACP, FACG, FINASIM
Date: 25 June 2024

[Coordinating Principal Investigator Acknowledgement]

Coordinating Investigator Acknowledgement

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I confirm that I have read the above protocol in the latest version. I understand in, and I agree that it contains all necessary details for carrying out the study as described.

I will make a reasonable effort to complete the study within the time designated.

I agree to conduct this clinical study in full accordance with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

Coordinating Principal Investigator

Prof. dr. Ari Fahrial Syam, SpPD, K-GEH, MMB, FACP, FACG, FINASIM
Date: 25 June 2024

[Investigator Acknowledgement – Site 01]

Investigator Acknowledgement

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[Investigator Acknowledgement – Site 02]

Investigator Acknowledgement

Protocol Title	A Multi-Center, Randomized, Open-Label Study to Evaluate Symptom Relief and Safety after Using Fexuprazan 40 Mg Compared to Esomeprazole 40 Mg in Patients with Gastroesophageal Reflux Disease (GERD).
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[Investigator Acknowledgement – Site 03]

Investigator Acknowledgement

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Principal Investigator

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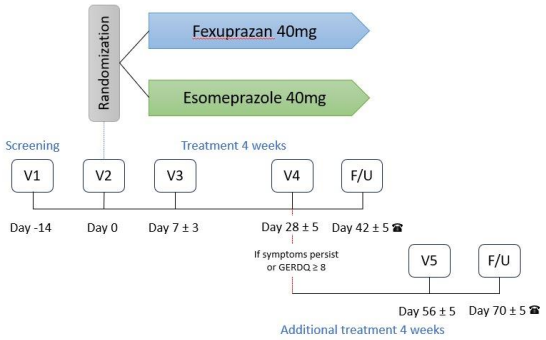
Date: 6/21/2024

[Protocol Synopsis]

Sponsor	Prof. Dr. dr. Ari Fahrial Syam, SpPD, K-GEH, MMB, FACP, FACG, FINASIM Collaborative partner : Daewoong Pharmaceutical Co. Ltd..
Study Title	A Multi-Center, Randomized, Open-Label Study to Evaluate Symptom Relief and Safety after Using Fexuprazan 40 Mg Compared to Esomeprazole 40 Mg in Patients with Gastroesophageal Reflux Disease (GERD).
Study center(s)	3 Study Center in Indonesia: 1. University of Indonesia Hospital 2. Islam Cempaka Putih Jakarta Hospital 3. Menteng Mitra Afia Jakarta Hospital
Study Period	• Study duration: Approximately 14 months from IRB approval to completion • Study duration for each subject: 8-12 weeks - Screening period: Up to 2 weeks - Treatment period: Up to 4 weeks (unhealed subject will continue additional 4 weeks of treatment) - Follow-up period: For 2 weeks from the last dose
Indication	Gastroesophageal Reflux Disease (GERD) patients
Objective	To evaluate symptom relief and safety after using Fexuprazan 40 mg compared to Esomeprazole 40 mg for patient with Gastroesophageal Reflux Disease (GERD).
Number of subjects	134 subjects
Study Design	A Multi-Center, Randomized, Open label, Double-arm, Controlled study, Investigator Initiated Trial
Study Methodology	Subjects will be provided a written informed consent to participate in the study and then undergo any screening. If a subject is taking any drug that affects the gastric mucosa at the time of screening, the treatment will be start after washout period of up to 2 weeks. Subjects who meet all of the inclusion criteria and none of the exclusion criteria based on the screening test results will be randomized. Overall, the subjects will receive treatment for a duration of 4 ~ 8 weeks., The subjects will take 1 tablet/capsule of the investigational product (IP) once daily (1 tablet of Fexuprazan 40 mg or 1 capsule Esomeprazole 40 mg according to randomization). Initially, the subject will received the IP for 1 week at Visit 2 (Day 0). Subject will visit the study site at Visit 3 (Day 7 ± 5 days) for early evaluation and will be prescribed for another 3 weeks of IP. Subjects will visit the study site at Visit 4 (Day 28 ± 5 days) to determine healing status through symptom relief. Healed subjects after 4 weeks of treatment will have a Safety Follow-Up (F/U) visit after 2 weeks, while unhealed subjects will continue with an additional 4 weeks of treatment. After unhealed subjects have completed a total of 8 weeks of treatment at Visit 5 (Day 56 ± 5 days), they will have a Safety F/U visit after 2 weeks. (This Safety F/U will be conducted over the phone. If necessary, additional examination and treatment may be performed according to the investigator's judgment.)  **Figure 1. Study Schematic**

Inclusion Criteria	Subjects must meet all the following criteria: 1) Male and female adults aged 18 to 60 years at the date of the written informed consent form. 2) Those who had experienced heartburn and/or acid regurgitation confirmed with: ➢ GERD-Q Score >7 and ➢ People who have experienced heartburn symptoms > 3 days within the last 7 days, or ➢ People who have experienced acid reflux (symptom of acid reflux or back flowing of contents from stomach into the esophagus) > 3 days within the last 7 days 3) Those who could understand the provided information and able to fill out the questionnaire and subject diary. 4) Those who voluntarily decided to participate in the study and wrote the informed consent form.
Exclusion Criteria	**[Digestive system related]** 1) Those who have been diagnosed with inflammatory bowel disease (Crohn disease, ulcerative colitis, etc.), primary esophageal motility, or pancreatitis. 2) Those who had a surgery to reduce gastric acid secretion or gastric or esophageal surgery (e.g., gastrotomy, mucosal resection, etc.), except appendectomy, cholecystectomy, or endoscopic polypectomy of benign polyps. 3) Those who had warning symptoms of malignant gastrointestinal tract such as odynophagia, severe dysphagia, bleeding, weight loss, anemia, or bloody stool. (But those who have additional warning symptoms besides typical symptoms of gastroesophageal reflux disease may be included if the result of endoscopy for verifying whether to have tumor is negative.) **[Medical history]** 4) Those who had a history of clinically significant disease of hepatic, renal, endocrine, hemato-oncologic, or urinary system. 5) Those who had history malignant tumor in the last 5 years. (But in case of malignant tumors except digestive malignant tumor, subjects completely healed for 5 years without recurrence are allowed to enroll.) 6) Those who had a history of psychosis, illegal drug, or alcohol abuse. 7) Those who had a known acquired immunodeficiency syndrome (AIDS) or hepatitis infection, including HBsAg+ or hepatitis C virus (HCV)-antibody-positive or virus carriers. (But the participant may be included in the study if he/she is HCV-RNA-negative). Rapid test screening will be done if there are no previous result. 8) Those who had hypersensitivity or history of clinically significant hypersensitivity reaction to investigational product. **[Medication history/treatment history]** 9) Those who received concomitant prohibition drugs within 2 weeks prior or need continuous treatment during the clinical study* (Those who meet the inclusion criteria following a sufficient wash-out period (2 weeks for NSAIDs with a half-life of > 24 hours) after taking the following drugs can be enrolled) - Non-steroidal anti-inflammatory drugs (aspirin, etc.) and acetaminophen : a low dose of aspirin (≤100 mg/day) which has been administered for the purpose of prevention before participating in the study is allowed. : acetaminophen administration is allowed up to 4 g/day and does not exceed 5 days in 4 weeks. - Acid suppressive drugs: Proton pump inhibitors (PPIs), PCAB, H2 receptor antagonists, anti-gastrin agents - Cholinergic drugs, anticholinergic drugs, and antispasmodics - Psychotropic drugs: Antipsychotics drugs, antidepressants, antimanic drugs, antianxiety drugs, and hallucinogenic agents, etc. - Steroids (allowed if used in a local application) - Antithrombotic drugs (antiplatelet drugs and anticoagulants) - Mucoprotective drugs 10) Those who need to take any prohibited concomitant medication during clinical study (Only Antacid and Prokinetic permitted as rescue drug. The use of Antacid and Prokinetic during the study period will be recorded as subject's prior/concomitant medication). 11) Those who took the other investigational product within 4 weeks prior to administration of investigational product. (But it is possible to enroll in the study [i.e., observational study,

	retrospective study] that doesn't affect this study's efficacy and safety as determined by the investigator.) **[Laboratory tests]** 12) At screening, those who had ① serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 2 X upper limit of normal ② serum creatinine or BUN ≥ 2 X upper limit of normal **[Others]** 13) Pregnant or breast-feeding women 14) Those who do not consent to use appropriate contraceptive methods during the study. - Appropriate contraceptive methods for patients or their partners - For Male subject: to use barrier method such as male condom and surgical sterilization such as vasectomy - For Female subject: to use 1) hormonal contraceptive such as Intraurine system : intrauterine hormone-containing system, implant, injection, contraceptive pills, or 2) non hormonal contraceptive such as Intraurine system : copper loop, barrier method : female condom, diaphragm or cervical cap, or surgical strerilization : tubectomy. 15) In the opinion of the investigator, those who were unsuitable for any reason.
Investigational product and mode of administration	**[Investigational Product]** ● Study drug: Fexuprazan tablet 40 mg ● Control drug: Esomeprazole capsule 40 mg **[Treatment period]** ● **Treatment 1: 4 weeks** A dose of Study drug or Control drug will be administered orally once daily without regard to meals for 4 weeks. The timing of administration should be kept consistent for each subject. ● **Treatment 2: Up to 8 weeks (4 weeks + 4 weeks)** Patients who have not been healed after the Treatment 1 of investigational product administration will have an additional 4-weeks of treatment period (Treatment 2) with the same mode of administration. Patients that categorized as a non-healed are those with a GERD-Q score >8.
Efficacy Endpoints	**[Primary efficacy endpoints]** 1. Proportions of subjects with symptoms relief at week 4 measured by GERD-Q Score <8 **[Secondary efficacy endpoints]** 1. Proportions of subjects with symptoms relief at week 8 measured by GERD-Q Score <8 (Week 8 evaluation will only be applicable to patient receiving treatment 2) 2. Assessment on symptoms based on the diary of subjects - The day to reach complete response (disappearance of heartburn, acid regurgitation, or heartburn/acid regurgitation for 7 consecutive days) after the first IP administration. - Proportions of subjects without the major symptoms (heartburn, acid regurgitation, or heartburn/acid regurgitation) for first 7 days, 4 weeks, and 8 weeks after the first IP administration. - Proportions of days free of major symptoms (heartburn, acid regurgitation, or heartburn/acid regurgitation) for first 7 days, 4weeks, and 8 weeks after the first IP administration (including all daytime, nighttime, and daytime/nighttime) 3. Assessment on symptoms of reflux disease (GERD-Q) - Changes from baseline in frequency by major symptom after 7 days, 4 weeks and 8 weeks. 4. Assessment of Quality of Life (GERD-HRQL: GERD-Health related quality life) - Changes from baseline in the total score of GERD-HRQL after 7 days, 4 weeks and 8 weeks. (Week 8 evaluation will only be applicable to patient receiving treatment 2) **[Exploratory endpoints]** Assessment on symptoms based on the diary of subjects. - Proportions of subjects who have not been awakened during sleep for heartburn or acid regurgitation for first 3 days, 7 days, 4 weeks, and 8 weeks (or based on the day Investigator's need) after the first IP administration.

	- Proportions of subjects who have relieved from chronic cough for first 3 days, 7 days, 4 weeks, and 8 weeks (or based on the day Investigator's need) after the first IP administration daytime and nighttime. - Proportions of subjects who have relieved from irritating feeling in the throat for full 3 days, 7 days, 4 weeks, and 8 weeks (or based on the day Investigator's need) after the first IP administration daytime and nighttime. (Week 8 evaluation will only be applicable to patient receiving treatment 2)
Safety Endpoints	1. Adverse events 2. Vital signs (blood pressure [diastolic/systolic], pulse rate, respiratory rate, and body temperature) 3. Physical examination (head to toe general physical examination) 4. Laboratory tests (hematology, blood chemistry, blood coagulation, urinalysis, liver function, renal Function)
Statistical Analysis Method	**[Primary efficacy endpoints]** The proportions of subjects with symptoms relief by Week 4 and their 95% confidence intervals will be provided by group. The proportions of subjects with symptoms relief by Week 4 will be calculated as the cumulative symptoms relief by using the results at the time of final observation including the Withdrawal visit. To compare the control group and study group, the lower bound of the 2-sided 95% confidence intervals will be obtained by using the Chi Square test or Fisher's Exact test method.. If this lower bound is greater than the non-inferiority margin of -0.1, the study group will be judged to be non-inferior to the control group. **[Secondary efficacy endpoints]** **1.** The proportions of subjects with symptoms relief by Week 8 and their 95% confidence intervals will be provided by group. The proportions of subjects with symptoms relief by Week 8 will be calculated as the cumulative symptoms relief by using the results at the time of final observation including the Withdrawal visit. To compare the control group and study group, the lower bound of the 2-sided 95% confidence intervals will be obtained by using the Chi Square test or Fisher's Exact test method. If this lower bound is greater than the non-inferiority margin of -0.1, the study group will be judged to be non-inferior to the control group. (Week 8 evaluation will only be applicable to patient receiving treatment 2) **2. Assessment on symptoms based on the diary of subjects**. - Complete Response (disappearance of heartburn, acid regurgitation, or heartburn/acid regurgitation for 7 consecutive days) is defined as the symptom score of 0 for 7 consecutive days for the first time after the first dose, and the survival time is defined as the time to reach Complete Response (CR) after the first IP administration. Kaplan-Meier plots will be drawn by treatment group, and the medians and their 2-sided 95% confidence intervals will be presented. To compare the control group and study group, the log-rank test will be used. - The number of subjects without any heartburn, acid regurgitation, or heartburn/acid regurgitation for the first 7 days, full 4 weeks, and full 8 weeks from the first IP administration, the proportion (%) of these subjects and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Chi Square test or Fisher's Exact test method. - Descriptive statistics (mean, standard deviation, median, minimum, and maximum) of the proportions of days free of any heartburn, acid regurgitation, or heartburn/acid regurgitation for the first 7 days, full 4 weeks, and full 8 weeks from the first IP administration will be presented for daytime, nighttime, and daytime/nighttime by group. For comparison between treatment groups, an ANCOVA model will be applied with treatment group as a treatment effect. The results of ANCOVA model will be summarized as the LSM differences between the study group and the control group, the corresponding 2-sided 95% confidence interval, and p-value. (Week 8 evaluation will only be applicable to patient receiving treatment 2)

	3. Assessment on symptoms of reflux disease using GERD-Q Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for the changes from baseline in frequency at the first 7 days, 4 weeks, and 8 weeks will be presented by time point. For the changes from baseline in variables measured at the first 7 days, 4 weeks, and 8 weeks after the IP administration, an ANCOVA model including treatment group as treatment effect, and baseline value will be applied. The results of ANCOVA model will be summarized as the least squares mean (LSM) and standard error by treatment group, the LSM differences between the study group and the control group, the corresponding 2-sided 95% confidence interval, and p-value. (Week 8 evaluation will only be applicable to patient receiving treatment 2) **4. Quality of life assessment using GERD-HRQL** Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for the changes from baseline in the total score of quality of life at the first 7 days, 4 weeks, and 8 weeks will be presented by time point. For the changes from baseline in variables measured at the first 7 days, 4 weeks, and 8 weeks after the IP administration, an ANCOVA model including treatment group as treatment effect, baseline values, and stratification factor (based on dominant symptoms in inclusion criteria: experiencing heartburn, regurgitation, or both more than >3 days in the last 7 days) as covariate will be applied. The results of ANCOVA model will be summarized as the least squares mean (LSM) and standard error by treatment group, the LSM differences between the study group and the control group, the corresponding 2-sided 95% confidence interval, and p-value. (Week 8 evaluation will only be applicable to patient receiving treatment 2) **[Exploratory endpoints]** **Assessment on symptoms based on the diary of subjects.** • The proportions (%) of subjects who have not been awakened during sleep for heartburn or acid regurgitation for the first 7 days, full 4 weeks, and full 8 weeks after the first IP administration and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Chi Square test or Fisher's Exact test method. • The proportions (%) of subjects who have relieved from chronic cough for the first 7 days, full 4 weeks, and full 8 weeks after the first IP administration and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Chi Square test or Fisher's Exact test method. • The proportions (%) of subjects who have relieved from foreign body sensation for the first 7 days, full 4 weeks, and full 8 weeks after the first IP administration and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Chi Square test or Fisher's Exact test method. (Week 8 evaluation will only be applicable to patient receiving treatment 2) **[Safety Endpoints]** All adverse events (AEs) will be standardized according to MedDRA version 21.0 (or higher). The frequency and percentage of subjects with at least 1 AE (or adverse drug reaction) will be presented by treatment group, and the 95% confidence intervals will be also presented. The frequency and percentage of subjects who are withdrawn due to serious adverse events or AEs will be presented and the listings will be provided. The descriptive statistics (mean, standard deviation, median, minimum, maximum, etc.) will be presented for continuous data, such as hematology, blood chemistry results, and vital signs by treatment group and visit; the frequency and percentage will be presented for categorical data, such as urinalysis and physical examination by category.

[Schedule of Study Activities]

	Screening (wash-out)	Treatment 1			Safety F/U[11)]	Treatment 2 (Unhealed Subject after 4 Weeks of Treatment	Safety F/U[11)]	Withdrawal Visit[12)]
Visit	**Visit 1[1)]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 4-1**	**Visit 5**	**Visit 5-1**	
Schedule	**Day-14 ~**	**Day 0**	**Day 7**	**Day 28**	**Day 42**	**Day 56**	**Day 70**	
Window	**-**	**-**	**±3day**	**±5day**	**±5day**	**±5day**	**±5day**	
Informed consent	O							
Demographic survey	O							
Assessment on symptom questionnaire (GERD-Q)[2)]	O	O	O	O		O[13)]		O[*)]
Quality of Life assessment (GERD-HRQL)		O	O	O		O[13)]		O[*)]
Medical and surgical history[3)]	O	O						
Prior/concomitant medications[4)]	O	O	O	O	O	O	O	O[12)]
Vital signs[5)]	O	O	O	O	O[11)]	O[13)]	O[11)]	O[12)]
Physical examination	O	O	O	O	O[11)]	O[13)]	O[11)]	O[12)]
Laboratory tests[6),7)]	O			O	O[11)]	O[13)]	O[11)]	O[12)]
Pregnancy test[6),8)]	O	O						
Inclusion/exclusion criteria[9)]		O						
Prescription of IPs[10)]		O	O	O[13)]				
Return of IPs and check of treatment compliance[10)]			O	O		O[13)]		O[12)]
Distribution of subject diary[10)]		O	O	O[13)]				
Collection of subject diary[10)]			O	O		O[13)]		O[12)]
Adverse events			O	O	O	O	O	O[12)]

1) Visit 1 and Visit 2 can be conducted on the same day.
2) Eligibility of subjects will be assessed based on the results from Visit 2 (GERD-Q result from Visit 1 will be used as the eligibility criteria). However, the results may be replaced with the test results obtained within 7 days prior to Visit 2, if available.
3) Gastrointestinal medical history and surgical history will be investigated at Visit 1 regardless of the time of previous occurrence and, for other medical history and surgical history, only those which occurred within 6 months from screening or are ongoing at screening and baseline will be investigated.
4) For prior medications, information on drugs administered within 4 weeks from the date of the written consent at Visit 1 will be collected. (Only Antacid and Prokinetic permitted as rescue drug)
5) Vital signs: After resting in a sitting position for 5 minutes or longer, blood pressure (diastolic/systolic), pulse rate, and body temperature will be measured.
6) The relevant tests can be replaced with the test results obtained from the same institution within 2 weeks from Visit 1, if available.
7) Laboratory tests will be conducted to check the inclusion/exclusion criteria and assess the safety (Visit 1, Visit 4, Visit 5, Withdrawal visit, and Safety F/U). At Visit 1, a re-test may also be conducted once according to the investigator's judgment and, in such a case, evaluation will be based on the result of re-test.

① Hematology	WBC with differential count (neutrophil, lymphocyte, monocyte, eosinophil, basophil), RBC, hemoglobin, hematocrit, platelets
② Blood Chemistry	Random blood glucose, ureum, uric acid, AST, ALT, creatinine, total bilirubin
③ Blood Coagulation test	PT, INR, APTT
④ Urinalysis	pH, specific gravity, albumin, bilirubin, glucose, urobilinogen, ketone, nitrite, occult blood, microscopy (urine RBC, urine WBC)

8) Pregnancy test will be performed with serum or urine pregnancy test will be performed at Visit 1. (Women who medically do not have child-bearing potential are exempt from the pregnancy test). If Visit 1 and Visit 2 are conducted on the same day, another pregnancy test (serum or urine test) should be conducted prior to IP administration even if the test result within 2 weeks before the date is available.
9) Eligibility of subjects will be assessed based on the results from Visit 2 (However GERD-Q result from Visit 1 will be used as the eligibility criteria).
10) Subjects who have not symptoms relief at Visit 4 will be prescribed the investigational product for treatment 2, and subject diary will be distributed to them. At Visit 5, treatment compliance will be checked, and subject diary will be collected only from those who have undergone Treatment 2.
(#: Subject diary completion will be checked at Visit 3, and appropriate training on diary keeping will be performed on the phone, if necessary.)
11) The Safety F/U will be conducted as a telephone visit within 2 weeks (± 5 days) from Last day of Visit 4 and Visit 5 only in subjects who complete all protocol-specific treatments, and the subjects may visit for additional tests or treatments based on the investigator's judgment.
12) If a subject decides to discontinue participation or is withdrawn from the study before completion, the Withdrawal visit procedures will take place within 2 weeks from the withdrawal decision. At the Withdrawal visit, the unused IPs or empty packaging will be returned, and the subject diary will be collected. However, assessment of Gastroesophageal Reflux Disease Questionnaire (GERD-Q)[*)] and quality of life questionnaire (GERD-HRQL)[*)] must be performed. If the patient refused to visit, above two Questionnaires can be done by telephone call and the document should be written on the EMR by the investigator.
13) Subjects who have not been healed after the Treatment 1 of investigational product administration will have an additional 4-weeks of treatment period (Treatment 2) with the same mode of administration.

[Abbreviations and Definition of Terms]

ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase, alanine
ANCOVA	Analysis of Covariance
APA	Acid pump antagonist
AST	Aspartate transaminase, aspartate
ATC	Anatomical therapeutic chemical
BUN	Blood urea nitrogen
BPOM	Indonesia Food and Drug Authority
Ca	Calcium
CUKB	Indonesia Good Clinical Practice
eCRF	Electronic case report form
FAS	Full analysis set
FSH	Follicle-stimulating hormone
gamma-GT	Gamma-glutamyl transpeptidase
GERD	Gastroesophageal reflux disease
GCP	Good clinical practice
Hb	Hemoglobin
HBs antigen	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HCV	Hepatitis C virus
HBS	Human immunodeficiency virus
HP-dog	Heidenhain pouch dog
ICH	International council for harmonization
IDMC	Independent data monitoring committee
IP	Investigational product
IRB	Institutional review board
K	Potassium
LPR	Lumen perfused rat
MedDRA	Medical dictionary for regulatory activities
Na	Sodium
LA grade	Los-Angeles grade
NSAIDs	Nonsteroidal anti-inflammatory drugs
P	Phosphorus
PM	Poor metabolizer
PPI	Proton pump inhibitor
PPS	Per protocol set
PT	Prothrombin time

PT	Preferred term
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical analysis system
SOC	System organ class
TEAE	Treatment emergent adverse event
UBT	Urease breath test
WBC	White blood cell

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1 Introduction

1.1 Background on Disease

Gastroesophageal Reflux Disease (GERD) is defined as a disorder caused by the repeated reflux of gastric contents into the esophagus, leading to disturbing symptoms and/or complications. The emphasis on the word "disturbing" was proposed by the Asia-Pacific Consensus on the Management of GERD in 2008 to highlight that GERD should be recognized as a disease due to its impact on the patient's quality of life. [1] The global pooled prevalence of GERD is approximately 13.98%, varying from 4.16% in China to 22.40% in Turkey, with the highest reported prevalence in a study conducted in Saudi Arabia (45.4%).[2] In Korea, the number of GERD patients increased by 11.6%, rising from 4,165,789 in 2016 to 4,650,302 in 2020. [3] Additionally, the number of outpatients at Korean medical hospitals increased by 40.4%, growing from 15,776 in 2016 to 22,155 in 2020. In Indonesia, a recent study conducted by Murdani et al. reported that 9.35% of the 278 subjects who participated in the study had GERD.[4] With the increasing prevalence of GERD worldwide, especially in Indonesia, a scientific consultation meeting with Key Opinion Leaders in Indonesian Gastroenterology is needed to identify the most effective and efficient treatment approaches.

1.2 Background on Existing Treatment

The recent Japanese GERD guidelines, issued by the Japan Society of Gastroenterology in 2021, propose the use of Potassium Competitive Acid Blocker (P-CAB) for both initial and maintenance treatment of mild Erosive Reflux Disease (ERD), in addition to PPI. The guidelines recommend using 4 weeks of P-CAB or 8 weeks of PPI as a first-line treatment for mild ERD. For patients with severe Erosive Reflux Disease, P-CAB is solely recommended as an initial treatment.[5] In the Seoul Consensus on the Diagnosis and Management of Gastroesophageal Reflux Disease 2020, it is mentioned that the efficacy of potassium-competitive acid blockers (P-CAB) is comparable to proton pump inhibitors (PPI). Therefore, they are recommended as an initial treatment for gastroesophageal reflux disease. [6]

In Indonesia, P-CAB hasn't been included in the Indonesian Guideline for GERD management. This is because Tegoprazan and Vonoprazan were recently launched in Indonesia (the latest Indonesian guideline for GERD is from 2014 with a small revision in 2019), and PPIs continue to be used as the first-line treatment.[7] Therefore, it is imperative for us to ascertain the necessity of Potassium Competitive Acid Blocker (P-CAB) as the latest treatment for gastric acid-related conditions in Indonesia through comprehensive consultations with Key Opinion Leaders (KOLs) in Indonesian Gastroenterology. This initiative is anticipated to yield invaluable insights guiding our strategic approach to future developments. Furthermore, given the recent introduction of P-CAB in Indonesia, it is of utmost importance to align our efforts with the interests of esteemed KOLs in Gastroenterology to ensure the timely update of the most recent version of the Indonesian Gastroesophageal Reflux Disease (GERD) management guideline. In this specific context, Fexuprazan may assume a pivotal role in shaping the afore mentioned guideline. Employing this systematic approach, our primary objective is to glean insightful perspectives on our product from distinguished Indonesian Gastroenterologist KOLs, enabling us to meticulously formulate a medical strategy that positions our offerings optimally within the Indonesian market.

1.3 Study Drug Profile

Fexuprazan is an antiulcer drug of APA class with a low molecular weight developed by Daewoong Pharmaceutical Co., Ltd. and has a unique chemical structure in comparison with other existing compounds. Fexuprazan has the mechanism of action that inhibits secretion of gastric acid by controlling potassium-dependently and reversibly H+ and K+ -ATPases within gastric parietal cells. Strong gastric acid secretion inhibition was confirmed in various acid secretion inhibition activity assessments performed in an in-vivo Fexuprazan study using a pylorus ligated rat model, lumen perfused rat (LPR) model, and heidenhain pouch dog (HP-dog) model. Also, the anti-ulcer efficacy of Fexuprazan was confirmed in reflux esophagitis and indomethacin-induced gastric injury model. Additionally, the possibility of oral administration was confirmed by analyzing the pathway of absorption, distribution, metabolism, and excretion via oral administration and the margin of safety was identified through toxicity tests in rodents/non-rodents.[9]

1.4 Prior Study Results

1) Phase 1 Study (DW_FEXUPRAZAN001)

A first in human study (FIH) in Korea was conducted in healthy male volunteers. In a single ascending dose study (n = 72), a single dose of 10, 20, 40, 80, 160, and 320 mg of Fexuprazan was administered in a fasted state with its corresponding dose of placebo in a double-blind manner to assess the safety, tolerability, and pharmacokinetics/pharmacodynamics and 20 and 40 mg of Esomeprazole were used as an active control to compare pharmacodynamic results with Fexuprazan.

To determine the impact of food, 160 mg was studied in a single dose and crossover study. No clinically significant change was found in physical examination, laboratory tests, vital signs, and electrocardiogram, the safety and tolerability endpoints. No SAE occurred and all AEs that occurred were mild (CTCAE 4.0 grade = 1) and were recovered without any special

treatment. A total of 7 adverse drug reactions (ADRs) with suspected causal relationship to Fexuprazan occurred which were epigastric discomfort, dyspepsia, and nausea (1 case each); vomiting and headache (2 cases each). Pharmacokinetic exposure of Fexuprazan oral administration increased more than dose proportionally (Supra-proportionality). In the assessment of pharmacodynamics based on the measurements of intragastric pH for 24 hours after administration of the investigational product, acid secretion within the stomach was inhibited more rapidly after a single administration of Fexuprazan than PPI, and the time during which intragastric pH remained ≥4 increased with dose escalation, indicating that gastric acid secretion inhibitory effect continued until nighttime with once-daily dosing. When administering Fexuprazan 160 mg before/after meal, no significant pharmacokinetic/pharmacodynamic change caused by food was observed.
In 7-day multiple ascending dose study (n = 48) conducted at doses of 20, 40, 80, and 160 mg after the single dose study, the safety and tolerability were confirmed for all doses. No SAE occurred and all AEs that occurred were mild (CTCAE 4.0 grade = 1) and were recovered without any special treatment. A total of 6 ADRs that were suspected to be causally related to Fexuprazan occurred which were abdominal distension, abdominal pain, skin exfoliation, headache, abdominal discomfort, and blood creatine phosphokinase increased (1 case each). After multiple doses of Fexuprazan during 7 days, the pharmacokinetic exposure increased dose-proportionally and the accumulation ratios resulting from multiple dosing were C_{max} = 0.91 to 1.24 and AUC_{tau} = 0.93 to 1.47. In the pharmacodynamic assessment, the percentage of time during which pH remained ≥4 in 24 hours was slightly increased after multiple dosing compared to single dosing, and Fexuprazan 40 mg showed the equivalent level of pharmacodynamics as Esomeprazole 40 mg.

2) Phase 2 Study (DW_FEXUPRAZAN002)
A multi-center, randomized, double-blind, active-controlled, phase 2, therapeutic exploratory study was conducted to evaluate the efficacy and safety of Fexuprazan by dose in patients with erosive gastroesophageal reflux disease in Korea.
In a total of 211 subjects, the results of having administered Fexuprazan 20 mg, 40 mg, 80 mg or Esomeprazole 40 mg once daily before meals for up to 8 weeks were as follows.
The proportions of subjects (FAS set) with mucosal breaks completely healed by Week 8 after administration of the IP, the primary efficacy endpoint, was 93.88% (46/49 subjects) in the Fexuprazan 20 mg group, 92.16% (47/51 subjects) in the Fexuprazan 40 mg group, 95.65% (44/46 subjects) in the Fexuprazan 80 mg group, and 97.92% (47/48 subjects) in the Esomeprazole 40 mg group. Since the lower limits of 95% confidence intervals for the differences in proportions of subjects with mucosal breaks completely healed between each Fexuprazan dose group and Esomeprazole 40 mg group were all larger than the non-inferiority margin of -15%, the effect of Fexuprazan treatment groups was confirmed to be non-inferior compared to the Esomeprazole 40mg group. In the assessment on major symptoms (heartburn and acid regurgitation) based on the diary of subjects, the secondary efficacy endpoint, the Fexuprazan groups showed symptom-alleviating effect in comparison with the Esomeprazole 40 mg group. In particular, the Fexuprazan 40 mg showed statistically significant difference in some assessments.
The ‘percentages (%) of subjects without any major symptoms during 7 days’ after starting the IP administration were 14.29% in the Fexuprazan 20 mg group, 21.57% in the Fexuprazan 40 mg group, 19.57% in the Fexuprazan 80 mg group, and 12.50% in the Esomeprazole 40 mg group, indicating no significant difference compared to the Esomeprazole 40 mg group. However, the ‘percentages (%) of days free of any major symptoms during 7 days’ after starting the IP administration were 32.14% in the Fexuprazan 20 mg group, 43.98% in the Fexuprazan 40 mg group, 37.89% in the Fexuprazan 80 mg group, and 28.27% in the Esomeprazole 40 mg group, indicating significant difference between the Fexuprazan 40 mg group and the Esomeprazole 40 mg group (p=0.0463). When the results of above were separately analyzed by dividing into daytime and nighttime, the ‘percentages (%) of daytime free of any major symptoms for 7 days’ indicated no statistically significant difference between the Fexuprazan groups and the Esomeprazole 40 mg group. However, the ‘percentages (%) of nighttime free of any major symptoms for 7 days’ were 41.96% in the Fexuprazan 20 mg group, 55.18% in the Fexuprazan 40 mg group, 48.76% in the Fexuprazan 80 mg group, and 33.63% in the Esomeprazole 40 mg group, indicating significant difference between the Fexuprazan 40 mg group and the Esomeprazole 40 mg group (p=0.0083). The ‘percentages (%) of days free of any major symptoms for 8 weeks’ indicated the same tendency with 49.41% in the Fexuprazan 20 mg group, 59.41% in the Fexuprazan 40 mg group, 55.65% in the Fexuprazan 80 mg group, and 42.88% in the Esomeprazole 40 mg group, indicating a significant difference between the Fexuprazan 40 mg group and the Esomeprazole 40 mg group (p=0.0283). When the results were separately analyzed by dividing into heartburn and acid regurgitation which were the major symptoms, the effect on the symptom of acid regurgitation showed no significant difference, but the percentage of days free of heartburn (7 days and 8 weeks) showed significant difference between Fexuprazan 40 mg and Esomeprazole 40 mg (p=0.0326 for the percentage of days free of heartburn during 7 days; p=0.0264 for the percentage of days free of heartburn during 8 weeks). Therefore, all Fexuprazan groups showed rapid improvement of symptoms and acid secretion inhibitory effects sustained until the nighttime. Especially, Fexuprazan 40 mg showed significant improvement of symptoms compared to Esomeprazole. The assessment of quality of life (GERD-HRQL) confirmed that the quality of life from symptoms were improved in all Fexuprazan groups.
The incidences of AEs and ADRs showed no statistically significant difference among treatment groups, and the events were all mild in severity and recovered without sequelae. One (1) case of moderate herpes zoster was reported as an SAE in the Esomeprazole 40 mg group, and no serious ADR, and AE and ADR resulting in death occurred during this study.

1.5 Assessment of Benefits and Risks

Reportedly, PPIs, the first-line therapy for diseases related to gastric acid secretion, takes 3 days or longer to make improvements in major symptoms (acid regurgitation and heartburn)[8]; their acid secretion inhibitory effects do not last until the nighttime[10]; and the genetic polymorphism of CYP2C19[11]causes variations in individual efficacy. Moreover, the regimen is restricted to be taken before a meal. Currently, drugs with APA mechanism are being developed to overcome these limitations of PPIs. The first phase I clinical study in healthy male adults confirmed that, unlike other PPIs that are activated under a strong acidic condition, Fexuprazan had a fast onset time and showed its acid secretion inhibitory effect that persisted until the nighttime since it had a reversible mechanism of action without activation by inhibiting the proton pump. Besides, since food does not have any significant effect on absorption of the drug, the patients can take the drug with or without having a meal, and it is expected that the patient's convenience of taking the drug can be improved.

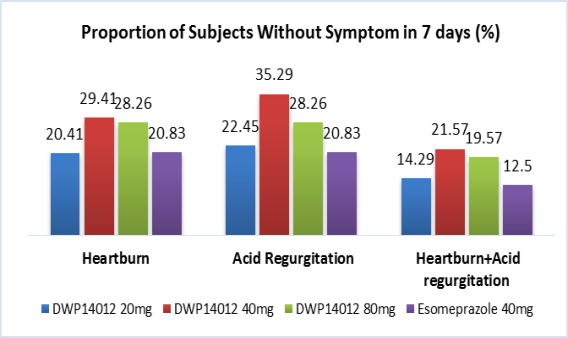
In the phase 2 study conducted in patients with erosive gastroesophageal reflux disease, healing of mucosal breaks in all Fexuprazan groups was non-inferior to the Esomeprazole 40 mg group, and no AE and ADR was noticeable in terms of safety. Also, Fexuprazan showed an effect of alleviating acid regurgitation and heartburn which are the major symptoms of gastroesophageal reflux disease during the treatment period.

Thus, the benefit expected from administration of Fexuprazan in patients with erosive gastroesophageal reflux disease, one of gastric acid secretion related diseases is considered to outweigh the risk, and a multi-center, randomized, double-blinded, active-controlled, phase 3, therapeutic confirmatory study was planned to assess the efficacy and safety of Fexuprazan in patients diagnosed with erosive gastroesophageal reflux disease.

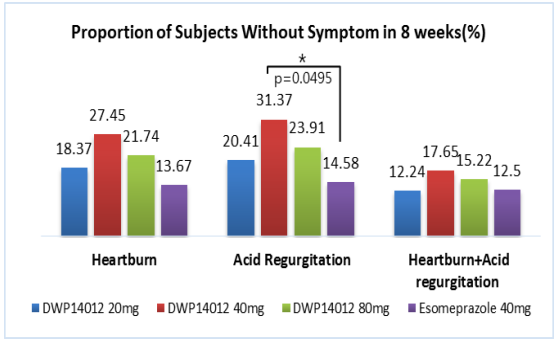
1.6 Rationale for Selection of Doses

A dose-finding study in patients with erosive gastroesophageal reflux disease confirmed that the Fexuprazan 40 mg had a similar safety profile to the Esomeprazole 40 mg group, it was non-inferior to the Esomeprazole 40 mg group for the proportions of subjects with mucosal breaks completely healed by Week 8, primary efficacy endpoint, and at the same time, it had a significant improvement of symptoms compared to the Esomeprazole 40 mg group.

For the ‘percentages (%) of subjects without the major symptoms for 7 days’ and ‘percentages (%) of subjects without the major symptoms during 8 weeks’ after initiation of the IP administration, the effect of Fexuprazan 20 mg was similar to Esomeprazole 40 mg. The percentages (%) of subjects without the major symptoms for 7 days and 8 weeks in the Fexuprazan 40 mg group and the Fexuprazan 80 mg group tended to be higher than the Esomeprazole 40 mg group. Therefore, rapid improvement of symptoms is expected from the Fexuprazan 40 mg or higher which is deemed to be based on the advantage of Fexuprazan with APA mechanism in which activation of proton pump is unnecessary whereas the PPI takes 3 days or longer from the drug administration to the onset of action.

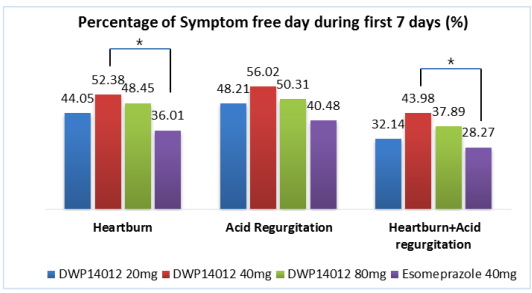


Percentages (%) of subjects without the major symptoms during 7 days

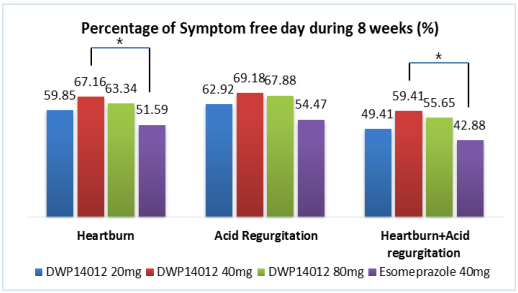


Percentages (%) of subjects without the major symptoms during 8 weeks

In addition, ‘percentages (%) of days free of any major symptoms for 7 days’ and ‘percentages (%) of days free of any major symptoms for 8 weeks’ tended to be higher in all Fexuprazan groups compared to the Esomeprazole 40 mg group. In particular, the Fexuprazan 40 mg group showed a statistically significant result compared to the Esomeprazole 40 mg group.

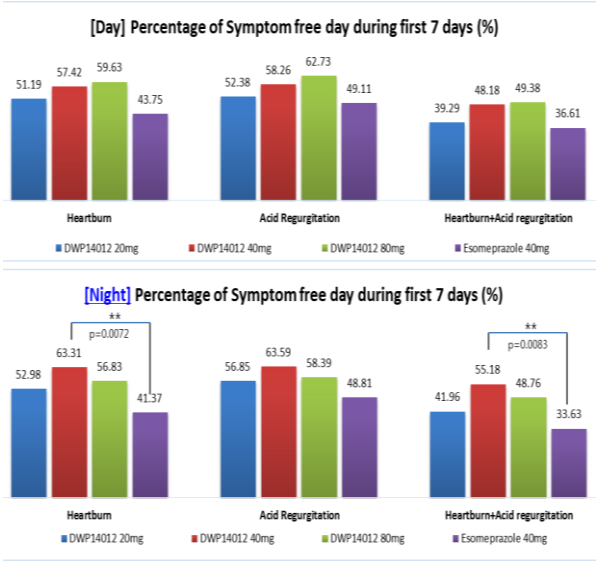


Percentages (%) of days free of each symptom for 7 days

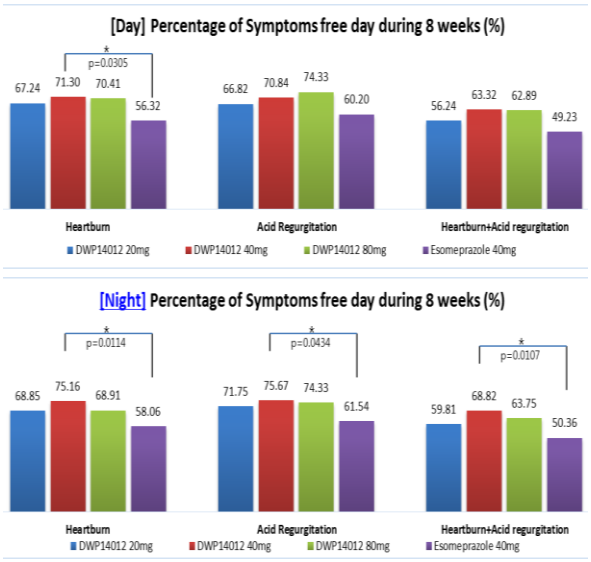


Percentages (%) of days free of each symptom for 8 weeks

When the results were analyzed by dividing into daytime and nighttime, the percentages of daytime for 7 days were not significantly different between the Fexuprazan dose groups and the Esomeprazole 40 mg group. However, Fexuprazan 40 mg showed a statistically significant difference in nighttime heartburn and heartburn + acid regurgitation compared to the control group. Therefore, it is considered that the difference in the symptom improvement resulted from acid secretion inhibitory effects sustained until the nighttime with Fexuprazan 40 mg once daily dosing. Also, no significant difference was seen from the daytime results for 8 weeks compared to the Esomeprazole 40 mg group, except for heartburn symptom. However, the Fexuprazan 40 mg showed statistically significant difference in all nighttime symptoms (heartburn, acid regurgitation, heartburn + acid regurgitation) for 8 weeks compared to the Esomeprazole 40 mg. Therefore, it can be said that Fexuprazan 40 mg significantly improves the symptoms during the treatment period because it has a rapid onset of action compared to the control group and its acid secretion inhibitory effects last until the nighttime.



Percentages (%) of days free of all major symptoms for 7 days



Percentages (%) of days free of all major symptoms for 8 weeks

With this study, it is intended to develop an acid pump antagonist that can address the unmet medical needs of PPIs which are slow onset of action and nocturnal acid rebound. In the phase 2 study, the assessment of primary efficacy endpoint showed that all Fexuprazan groups were non-inferior to the control group and did not show difference among the dose groups, but it is expected that Fexuprazan 40 mg and higher dose would show difference in symptom improvement. Therefore, the phase 3 dose was set at Fexuprazan 40 mg to confirm the efficacy and safety in patients with erosive gastroesophageal reflux disease.

2 Study Objective

This study is to evaluate symptom relief after using Fexuprazan 40 mg compared to Esomeprazole 40 mg for patient with Gastroesophageal Reflux Disease (GERD).

3 Study Population

3.1 Target Number of Subjects

The number of subjects to demonstrate non-inferiority of the study group compared to the control group with 80% power using a non-inferiority margin of -0.1 at one-sided significance level of 2.5%, considering a 20% dropout rate, a total of 134 subjects will be needed.

3.2 Inclusion Criteria

Subjects must meet all the following criteria:

1) Male and female adults aged 18 to 60 years at the date of the written informed consent form.
2) Those who had experienced heartburn and/or acid regurgitation confirmed with:
   a. GERD-Q Score >7 and
   b. People who have experienced heartburn symptoms > 3 days within the last 7 days, or
   c. People who have experienced acid reflux (symptom of acid reflux or back flowing of contents from stomach into the esophagus) > 3 days within the last 7 days
3) Those who could understand the provided information and able to fill out the questionnaire and subject diary.

4) Those who voluntarily decided to participate in the study and wrote the informed consent form.

3.3 Exclusion Criteria

[Digestive system related]

1) Those who have been diagnosed with inflammatory bowel disease (Crohn disease, ulcerative colitis, etc.), primary esophageal motility, or pancreatitis.
2) Those who had a surgery to reduce gastric acid secretion or gastric or esophageal surgery (e.g., gastrotomy, mucosal resection, etc.), except appendectomy, cholecystectomy, or endoscopic polypectomy of benign polyps.
3) Those who had warning symptoms of malignant gastrointestinal tract such as odynophagia, severe dysphagia, bleeding, weight loss, anemia, or bloody stool.
   (But those who have additional warning symptoms besides typical symptoms of gastroesophageal reflux disease may be included if the result of endoscopy for verifying whether to have tumor is negative.)

[Medical history]

4) Those who had a history of clinically significant disease of hepatic, renal, endocrine, hemato-oncologic, or urinary system.
5) Those who had history malignant tumor in the last 5 years.
   (But in case of malignant tumors except digestive malignant tumor, subjects completely healed for 5 years without recurrence are allowed to enroll.)
6) Those who had a history of psychosis, illegal drug or alcohol abuse.
7) Those who had a known acquired immunodeficiency syndrome (AIDS) or hepatitis infection, including HBsAg+ or hepatitis C virus (HCV)-antibody-positive or virus carriers.
   (But the participant may be included in the study if he/she is HCV-RNA-negative). Rapid test screening will be done if there are no previous result.
8) Those who had hypersensitivity or history of clinically significant hypersensitivity reaction to investigational product.

[Medication history/treatment history]

9) Those who received concomitant prohibition drugs within 2 weeks prior or need continuous treatment during the clinical study[*)]
   *) Those who meet the inclusion criteria following a sufficient wash-out period (2 weeks for NSAIDs with a half-life of > 24 hours) after taking the following drugs can be enrolled)
   a. Non-steroidal anti-inflammatory drugs (aspirin, etc.) and acetaminophen: a low dose of aspirin (≤100 mg/day) which has been administered for the purpose of prevention before participating in the study is allowed: acetaminophen administration is allowed up to 4 g/day and does not exceed 5 days in 4 weeks.
   b. Acid suppressive drugs: Proton pump inhibitors (PPIs), PCAB, H2 receptor antagonists, anti-gastrin agents
   c. Cholinergic drugs, anticholinergic drugs, and antispasmodics
   d. Psychotropic drugs: Antipsychotics drugs, antidepressants, antimanic drugs, antianxiety drugs, and hallucinogenic agents, etc.
   e. Steroids (allowed if used in a local application)
   f. Antithrombotic drugs (antiplatelet drugs and anticoagulants)
   g. Mucoprotective drugs
10) Those who need to take any prohibited concomitant medication during clinical study. (Only Antacid and Prokinetic permitted as rescue drug. The use of Antacid and Prokinetic during the study period will be recorded as subject's prior/concomitant medication)
11) Those who took the other investigational product within 4 weeks prior to administration of investigational product.
    (But it is possible to enroll in the study [i.e., observational study, retrospective study] that doesn't affect this study's efficacy and safety as determined by the investigator.)

[Laboratory tests]

12) At screening, those who had
    a. serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 2 X upper limit of normal
    b. serum creatinine or BUN ≥ 2 X upper limit of normal

[Others]

13) Pregnant or breast-feeding women
14) Those who do not consent to use appropriate contraceptive methods during the study.
    Appropriate contraceptive methods for patients or their partners:
    - For Male subject: to use barrier method such as male condom and surgical sterilization such as vasectomy;

    - For Female subject: to use 1) hormonal contraceptive such as Intraurine system : intrauterine hormone-containing system, implant, injection, contraceptive pills, or 2) non hormonal contraceptive such as Intraurine system : copper loop,

barrier method : female condom, diaphragm or cervical cap, or surgical strerilization : tubectomy.

15) In the opinion of the investigator, those who were unsuitable for any reason.

3.4 Criteria for Withdrawal

The subjects are allowed to spontaneously discontinue participation in this study at any time. The investigator may discontinue participation of a subject in this study at any time as per the subject's decision. However, a subject who are terminated early for showing a sufficient level of efficacy of the investigational product will not be considered as a withdrawal. If a subject is withdrawn from the study, the study results obtained from the discontinued/withdrawal case until the time point of discontinuation/withdrawal may be reviewed for evaluable items at the final evaluation.

In following cases, the investigator may withdraw the subject from the study.

1) Violation of inclusion/exclusion criteria is identified during the study.
2) Subjects are considered difficult to continue with the study due to adverse events as per the investigator's decision.
3) Subjects have received or are deemed to require medications or treatments that may affect the study results during treatment period or follow-up period.
4) Voluntary consent withdrawal by the subject or subject's legally acceptable representatives.
5) Subjects cannot not cooperate with the investigator.
6) Lost to follow-up.
7) The investigator decides to withdraw subjects.
8) Subject is pregnant during the study

If a subject determines to discontinue his/her participation and withdrawn from the study prior to completion, procedures scheduled for the Withdrawal visit should be performed. The procedure for the Withdrawal visit will be conducted within 2 weeks after the withdrawal decision is made. At the Withdrawal visit, the unused IPs or empty packaging will be returned, and the subject diary will be collected.
If the patient refused to visit, the vital sign, physical examination and lab test can be exclude. However, assessment of Gastroesophageal Reflux Disease Questionnaire (GERD-Q) and quality of life questionnaire (GERD-HRQL) must be performed at least by telephone call by the investigator, and all document should be written on the EMR by the investigator.s.
To prevent any missing AEs that the investigator is not aware of, all kinds of methods must be employed to directly contact the subjects who refuse to visit such as phone call, letter, or personal visit. Any withdrawn subject cannot participate in the same study again.

4 Description of Study Design

4.1 Study Period

• Study duration: Approximately 14 months from IRB approval to completion
• Study duration for each subject: 8-12 weeks
  - Screening period: Up to 2 weeks
  - Treatment period: Up to 4 weeks (unhealed subject will continue additional 4 weeks of treatment)
  - Follow-up period: For 2 weeks from the last dose

4.2 Study Design

A Multi-Center, Randomized, Open label, Double-arm, Controlled study, Investigator Initiated Trial.

4.3 Rationale for Study Design

4.3.1 Rationale for Establishment of Efficacy Endpoints

The clinical study guidelines for gastroesophageal reflux disease treatments requires 4 to 8 weeks of treatment period in general. In Indonesian guideline, Gastroesophageal Reflux Disease (GERD) is diagnosed by GERD Q score > 7, so the proportion of subject with symptom relief indicator is indicated by GERD-Q <8 [7,12,13]
Also, typical symptoms of gastroesophageal reflux disease are heartburn and acid regurgitation and the clinical study guidelines for gastroesophageal reflux disease treatments specifies to include endpoints for evaluating disappearance of such symptoms. [12] Assessment on symptoms includes severity and frequency and, since symptom assessment by physicians or investigators is less reliable, the subjects have to assess their symptoms by themselves.[12] Given that, this study sets the assessment on symptoms based on the diary of subjects as a secondary efficacy endpoint.

4.3.2 Rationale of Establishment of Treatment Period

In accordance with the clinical study guideline for gastroesophageal reflux disease treatments, 4 to 8 weeks of treatment period is generally recommended in a clinical study on gastroesophageal reflux disease [12,13] and this study set 4 weeks of

dosing period in consideration of dosing periods in other clinical studies on gastroesophageal reflux disease. [14,15,16]

4.3.3 Rationale of the Dosing Interval

In a phase 1 clinical study performed in Korea, the elimination half-life in blood of Fexuprazan was 9 hours and acid secretion suppression were maintained until the nighttime with once-daily dosing. Also, in the phase 2 study conducted in patients with erosive gastroesophageal reflux disease, Fexuprazan 40 mg was administered once daily for up to 8 weeks, and it was effective in endoscopic healing and alleviating the symptoms. Especially, the symptoms were improved faster than the active control, Esomeprazole 40 mg group, and the nighttime symptoms were also improved effectively. Therefore, the dosing interval of Fexuprazan was set with once-daily dosing as with the active control.

4.4 Randomization Method

This clinical study is an open label trial.The randomization list will be prepared by an independent party from PT Equilab International and reviewed by PT Equilab International's consultant. The investigational product (IP) will be dispensed by an independent party who has qualification as pharmacist prior to dosing day. The site study pharmacist will administer the dispensed IP to the subjects based on the randomization. The randomization will be balanced and the randomization code will be kept under controlled access. If a subject provides a written consent to participate in this clinical study, screening number will be assigned, and subjects who meet all the inclusion criteria and none of the exclusion criteria based on the screening test results will be assigned to randomization numbers and randomized in a 1:1 ratio to one of study group or control group.

The randomization number will be denoted by for example, '00RXXX' (ex.01R001)and means the following.

- '00': means site number.
  - 01: RS. University of Indonesia
  - 02: RS. Islam Cempaka Putih
  - 03: RS. MMA
- 'R': means randomization.
- 'XXX': order of randomized subjects

5 Criteria for Completion and Early Termination of Study

5.1 Scheduled Completion

If all protocol-specified procedures and assessments are completed after the IP administration, the subject will be considered to have completed the study. Subjects with symptoms relief at Week 4 measured by GERD-Q Score <8 will have the Safety F/U after 2 weeks from the date and be terminated from the study.
In this study, completion of the last subject is defined as the end of study.

5.2 Early Termination

The sponsor may terminate the study early in overall or at specific study sites. Reasons for termination of the study by the sponsor are as follows:

1) Failure to meet expected enrollment goals in overall or at specific study sites.
2) Emergence of any efficacy/safety information that may significantly affect continuation of the study.
3) Violation of Good Clinical Practice (GCP), the protocol, or the contract by a study site or the investigator, disturbing the appropriate conduct of the study.
4) Any other administrative reasons that may affect continuation of the study.

The investigator and Institutional Review Board may terminate the study when they determine that the benefits that individuals and the society may gain do not outweigh or justify the risks and discomforts, based on information observed and collected during the study.

6 Identity and Management of Investigational Products

6.1 Investigational Products

6.1.1 Study Drug

The investigational product Fexuprazan is a green, oval-shaped film-coated tablet. Drug substance and content for each tablet are as follows:

1) Code Name: Fexuprazan
2) Dosage form and appearance: green, oval-shaped film-coated tablet
3) Drug substances and their contents:

Compounding purpose	Ingredient name/Weight	Specification	Content

Active ingredient	FEXUPRAZAN/624 mg	Self-specification	40.00 mg

4) Storage condition: Store in a tight container at room temperature (1–30℃)

6.1.2 Control drug

Commercially available esomeprazole, as a treatment for gastroesophageal reflux disease, is selected as the control drug for this study and its product name, content, dosage form, etc. are as follows:

1) Product name (Ingredient name): ESOFERR (Esomeprazole 40mg)
2) Dosage form and appearance: Hard gelatin capsule, Buff opaque with Dexa logo (black), contain off-white to greyish pellets
3) Drug substances and their contents:

Compounding purpose	Ingredient name	Content
Active ingredient	Esomeprazole	40 mg

4) Storage condition: Store in a tight container at room temperature (1–30℃)

6.2 Administration Route and Method of Investigational Products

For maximum 4 weeks from the next day of investigational product prescription, 1 tablet/capsule will be administered orally once daily without regard to meals. Tablets/capsules should be taken at a regular time, if possible.

6.3 Labeling and Packing of Investigational Product

The investigational products (IPs) will be manufactured and packaged by Daewoong Pharmacutical Co., Ltd, a South Korean Pharmaceutical company located at 1, Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea, and then imported to the assigned Clinical Research Organization – PT. Equilab International which office is located at Jl. RS. Fatmawati Persil 33, RT.2/RW.5, West Cilandak, Cilandak, South Jakarta, 12430, Indonesia and delivery to the clinical trial pharmacists at each of the study sites.

For IP labeling, the following information is labeled on the packaging of the IP, as detailed in Indonesian Food and Drug Authority Regulation:

1) A statement that it can only be used for the purpose of clinical study (e.g., “For clinical use only”).
2) Investigational product name or identification mark (state study drug and control drug for open label study).
3) Batch number for identifying contents and packaging job.
4) Protocol Number.
5) Quantity of dosage units.
6) Dispense date or visit number.
7) Subject number and initials.
8) Route of administration.
9) Additional information: Storage condition, expire date, etc.

6.4 Dispensing, Storage, Accountability and Recording of Investigational Product

The assigned CRO will deliver the IPs to the principal investigator or clinical trial pharmacist designated by the principal investigator of each study site. The clinical trial pharmacist should be aware of any receipt, volume of shipment, and condition of IPs and retain records of receipt, dispensing, and return of the IPs.

6.4.1 Dispensing

Dispensing of any products used for the study should be done based on the prescription signed by the principal investigator or sub-investigators who are participating in this study.

6.4.2 Storage Conditions and Accountability

The principal investigator and clinical trial pharmacist of study site are responsible for managing the IPs.

The assigned CRO will deliver the IPs to the clinical trial pharmacist, and the clinical trial pharmacist is in charge for receipt, inventory control, subject-by-subject dispensing, and return of the IPs, record relevant details, and inform relevant information to the principal investigator periodically.

The clinical trial pharmacist or the principal investigator or sub-investigator who controls IPs will record the date of dispensing, quantity, batch or serial number, and expiry or use-by date of IPs, IP number and randomization number (or screening number) for each subject in the drug accountability logs, and store and maintain them. The clinical trial pharmacist should complete dosing records to confirm each subject has received appropriate dosage specified in the protocol and should verify that IP inventory matches documented inventory.

The principal investigator should ensure that IPs are administered and managed in accordance with the protocol.

The IPs will be stored under storage conditions (room temperature, tight container) as determined by the manufacturer in a secure, limited-access storage area. In case any concern about the quality of the IPs is suspected or raised, the IPs should not be administered, and the sponsor should be notified promptly.
The study monitor will periodically access the management records to check the history of IP use and storage status.
The investigator must not use the IPs and relevant materials for any purpose other than protocol specifics.

6.4.3 Returns and Destruction

If any IP is discarded or lost in the study site, the manager will record relevant details in the IP accountability log. In principle, disposal of the IPs at the study site is not allowed. When the study ends, any unused IPs that have not been administered to the subjects or returned by the subjects after administration should be returned to the assigned CRO or the location specified by the sponsor. A certificate of return should be attached when sending the IPs to confirm any drugs to be returned.

7 Study Methodology and Dosing Schedule

7.1 Overall Study Methodology

Screening Period

Subjects will provide written informed consent to participate in the study and then undergo any screening. Subjects who meet all the inclusion criteria and none of the exclusion criteria based on the screening test results will be included into the study,

Treatment Period

The subject will receive the IP consumed once daily for 1 week at Visit 2 (Day 0). Subjects will have a site visit 1 week after IP administration and prescribed the IP for another 3 weeks at Visit 3 (Day 7 ± 5 days). Subjects will visit the study at Visit 4 (Day 28 ± 5 days) to determine healing status by Gastroesophageal Reflux Questionnaires (GERD-Q).
Subjects who have not been healed at Visit 4 (Day 28 ± 5 days) will have an additional IP administration period for 4 weeks and then visit the study site at Visit 5 (Day 56 ± 5 days) to determine healing status.
If, a subject withdrawn during the treatment period will visit the study site within 2 weeks from the withdrawal decision and undergo the Withdrawal visit procedures. However, they will not be conducted if the subject refuses them.

Follow up Period

Subjects will have a Safety F/U visit within 2 weeks (± 5 days) from the day when healing is confirmed. (However, this visit will be carried out by a telephone visit. If necessary, additional examination and treatment may be performed according to the investigator's judgment.)

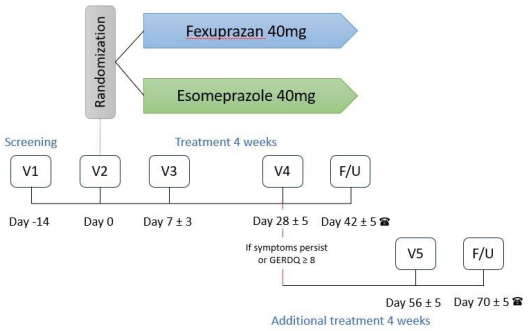


Figure 2. Study Schematic

7.2 Dosage, Administration and Duration of Investigational Product

7.2.1 Dosage and Duration of Administration

① Study group (Fexuprazan 40 mg)
- Fexuprazan 40 mg 1 tablet

② Control group (Esomeprazole 40 mg)
- Esomeprazole 40 mg 1 capsule

7.2.2 Administration Method

For maximum 8 weeks from the next day of investigational product dispensing, 1 tablet/capsule will be administered orally once daily without regard to meals. Tablets/Capsules should be taken at a regular time.

7.3 Concomitant and Prohibited Therapies

7.3.1 Permitted Concomitant Therapies

Concomitant therapies (medication or treatment) unless included in the prohibited medications may be implemented if medically indicated at the discretion of the investigator. Ingredient name (or brand name), regimen and dosage (amount of 1 dose, dose unit, frequency of administration, route of administration), duration of administration (start date of administration, during administration, end date of administration), and purpose of concomitant medication taken during the study should be recorded on the case report form. Only Antacid and Prokinetic permitted as rescue drug.

7.3.2 Concomitant and Prohibited Therapies

- Non-steroidal anti-inflammatory drugs (aspirin, etc.) and acetaminophen
  : a low dose of aspirin (≤100 mg/day) which has been administered for the purpose of prevention before participating in the study is allowed
  : acetaminophen administration is allowed up to 4 g/day and does not exceed 5 days in 4 weeks
- Acid suppressive drugs: Proton pump inhibitors (PPIs), acid pump antagonists, H2 receptor antagonists, anti-gastrin agents
- Cholinergic drugs, anticholinergic drugs, and antispasmodics
- Psychotropic drugs: Antipsychotics drugs, antidepressants, antimanic drugs, antianxiety drugs, and hallucinogenic agents, etc.
- Steroids (allowed if used in a local application)
- Antithrombotic drugs (antiplatelet drugs and anticoagulants)
- Mucoprotective drugs

7.3.3 Treatment Compliance

In order to ensure the validity of research data related to the ability of IP to relieve symptoms and ensure safety in subjects, also to gain a better understanding of drug performance in real-world settings and improve the quality of study outcomes, at each visit after the administration of the IP, all subjects should return the unused IP prescribed at the previous visit and empty packaging, and the sub-investigator (or a designee) will check the number of tablets/capsule to be taken, number of tablets/capsules actually taken, and number of returned and unreturned tablets/capsules and record them on the case report form at each visit.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets/capsules actually taken}}{\text{Number of tablets/capsules to be taken}} \times 100$$

8 Study Procedures and Assessments

8.1 Visit Schedule

Subjects will provide written informed consent to participate in the study and then undergo any screening. Subjects who meet all of the inclusion criteria and none of the exclusion criteria based on the screening test results will be included into the study. Subjects will have a site visit 1 week after IP administration. Subjects will visit the study site again in person 4 weeks after the first IP administration to determine healing status with symptoms relief at Week 4 measured by GERD-Q Score <8. Healed subjects will have a Safety F/U visit after 2 weeks (± 5 days) and unhealed subjects will take the IP for additional 4 weeks and then visit the site to determine healing status with symptoms relief at Week 8 measured by GERD-Q Score <8. The Safety F/U visit will be conducted 2 weeks (± 5 days). The Safety F/U visit will be conducted via telephone visit and subjects will have a visit for additional tests or treatments based on the investigator's judgment.
In the event of withdrawal, the procedures for the Withdrawal visit will also be conducted by visiting the site within 2 weeks after the withdrawal decision is made. See Study Schedule Table for procedures to be performed at each visit.

8.2 Study Schedule Table

	Screening (wash-out)	Treatment 1			Safety F/U[11)]	Treatment 2 (Unhealed Subject after 4 Weeks of Treatment	Safety F/U[11)]	Withdrawal Visit[12)]
Visit	**Visit 1[1)]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 4-1**	**Visit 5**	**Visit 5-1**	

Schedule	Day-14~	Day 0	Day 7	Day 28	Day 42	Day 56	Day 70	
Window	-	-	±3day	±5day	±5day	±5day	±5day	
Informed consent	O							
Demographic survey	O							
Assessment on symptom questionnaire (GERD-Q)[2)]	O	O	O	O		O[13)]		O[*)]
Quality of Life assessment (GERD-HRQL)		O	O	O		O[13)]		O[*)]
Medical and surgical history[3)]	O	O						
Prior/concomitant medications[4)]	O	O	O	O	O	O	O	O[12)]
Vital signs[5)]	O	O	O	O	O[11)]	O[13)]	O[11)]	O[12)]
Physical examination	O	O	O	O	O[11)]	O[13)]	O[11)]	O[12)]
Laboratory tests[6),7)]	O			O	O[11)]	O[13)]	O[11)]	O[12)]
Pregnancy test[6),8)]	O	O						
Inclusion/exclusion criteria[9)]		O						
Prescription of IPs[10)]		O	O	O[13)]				
Return of IPs and check of treatment compliance[10)]			O	O		O[13)]		O[12)]
Distribution of subject diary[10)]		O	O	O[13)]				
Collection of subject diary[10)]			O	O		O[13)]		O[12)]
Adverse events			O	O	O	O	O	O[12)]

1) Visit 1 and Visit 2 can be conducted on the same day.
2) Eligibility of subjects will be assessed based on the results from Visit 2 (GERD-Q result from Visit 1 will be used as the eligibility criteria). However, the results may be replaced with the test results obtained within 7 days prior to Visit 2, if available.
3) Gastrointestinal medical history and surgical history will be investigated at Visit 1 regardless of the time of previous occurrence and, for other medical history and surgical history, only those which occurred within 6 months from screening or are ongoing at screening and baseline will be investigated.
4) For prior medications, information on drugs administered within 4 weeks from the date of the written consent at Visit 1 will be collected. (Only Antacid and Prokinetic permitted as rescue drug)
5) Vital signs: After resting in a sitting position for 5 minutes or longer, blood pressure (diastolic/systolic), pulse rate, and body temperature will be measured.
6) The relevant tests can be replaced with the test results obtained from the same institution within 2 weeks from Visit 1, if available.
7) Laboratory tests will be conducted to check the inclusion/exclusion criteria and assess the safety (Visit 1, Visit 4, Visit 5, Withdrawal visit, and Safety F/U). At Visit 1, a re-test may also be conducted once according to the investigator's judgment and, in such a case, evaluation will be based on the results of re-test.

① Hematology	WBC with differential count (neutrophil, lymphocyte, monocyte, eosinophil, basophil), RBC, hemoglobin, hematocrit, platelets
② Blood Chemistry	Random blood glucose, ureum, uric acid, AST, ALT, creatinine, total bilirubin
③ Blood Coagulation test	PT, INR, APTT
④ Urinalysis	pH, specific gravity, albumin, bilirubin, glucose, urobilinogen, ketone, nitrite, occult blood, microscopy (urine RBC, urine WBC)

8) Pregnancy test will be performed with serum or urine pregnancy test will be performed at Visit 1. (Women who medically do not have child-bearing potential are exempt from the pregnancy test). If Visit 1 and Visit 2 are conducted on the same day, another pregnancy test (serum or urine test) should be conducted prior to IP administration even if the test result within 2 weeks before the date is available.
9) Eligibility of subjects will be assessed based on the results from Visit 2 (However GERD-Q result from Visit 1 will be used as the eligibility criteria).
10) Subjects who have not symptoms relief at Visit 4 will be prescribed the investigational product for treatment 2, and

subject diary will be distributed to them. At Visit 5, treatment compliance will be checked, and subject diary will be collected only from those who have undergone Treatment 2.
(#: Subject diary completion will be checked at Visit 3, and appropriate training on diary keeping will be performed on the phone, if necessary.)

11) The Safety F/U will be conducted as a telephone visit within 2 weeks (± 5 days) from Visit 4 only in subjects who complete all protocol-specific treatments, and the subjects may visit for additional tests or treatments based on the investigator's judgment.
12) If a subject decides to discontinue participation or is withdrawn from the study before completion, the Withdrawal visit procedures will take place within 2 weeks from the withdrawal decision. At the Withdrawal visit, the unused IPs or empty packaging will be returned, and the subject diary will be collected. However, assessment of Gastroesophageal Reflux Disease Questionnaire (GERD-Q)*) and quality of life questionnaire (GERD-HRQL)*) must be performed. If the patient refused to visit, above two Questionnaires can be done by telephone call and the document should be written on the EMR by the investigator.
13) Subjects who have not been healed after the Treatment 1 of investigational product administration will have an additional 4-weeks of treatment period (Treatment 2) with the same mode of administration.

8.3 Enrollment and Clinical Assessment

8.3.1 Obtaining Written Consent and Assigning Screening Numbers

Prior to any tests or procedures associated with this study, all information about the study should be provided to the subjects using a subject information sheet, and the informed consent form containing the subject name, signature, and date of signing will be obtained. A screening number will be assigned in order of written consent obtained from subjects.
The screening number will be denoted by for example, '00SXXX' (ex. 01S001) and means the following.

- '00': means site number
  - 01 : RS. University of Indonesia
  - 02 : RS. Islam Cempaka Putih
  - 03 : RS. MMA
- 'S': means screening
- 'XXX': order of subjects to be participating at each site

8.3.2 Demographic Information

At the screening visit (Visit 1), the followings will be investigated:

- Initial
- Month and year of birth (age)
- Gender
- Smoking history
- Drinking history

8.3.3 Questionnaire assessment

- Gastroesophageal Reflux Disease Questionaries (GERD-Q) (See Appendix 3)
  - The subject will complete the GERD-Q at the screening visit (Visit 1) and Visit 2. The test results from Visit 1 will be used as the basis to determine eligibility for inclusion/exclusion.
  - The subjects who meet the inclusion criteria will complete the GERD-Q at Visit 3, Visit 4, and Visit 5.
- Quality of Life assessment (GERD-Health Related Quality of Life, GERD-HRQL) (See Appendix 4)
  - The subjects who meet the inclusion criteria will complete the GERD-HRQL questionnaire at Visit 2, Visit 3, Visit 4 and Visit 5.[19, 20. 21]

8.3.4 Medical/surgical history

Gastrointestinal medical history and surgical history will be investigated at the screening visit (Visit 1) regardless of the time of previous occurrence and, for other medical history and surgical history, only those which occurred within 6 months from screening or are ongoing at screening and baseline will be investigated. Any clinically significant medical conditions or abnormal conditions ongoing at screening will be investigated, and their diagnosis and persistence will be recorded on the case report form.

8.3.5 Prior/Concomitant Medications

Prior medications will be collected for the drugs administered within 4 weeks prior to the written consent at Visit 1, and concomitant medications will be collected for the drugs that have been administered since the administration of the IP.

8.3.6 Vital signs

The followings will be measured in a seated position after resting for 5 minutes at the screening visit (Visit 1), Visit 2, and Visit 4. Any clinically significant abnormalities prior to the administration of the IP will be recorded in the medical history section, and any clinically significant abnormalities after the administration of the IP will be recorded in the adverse events section.

- Blood pressure (systolic/diastolic)
- Pulse rate
- Body temperature

8.3.7 Physical examination

The investigator will measure the height, weight and the BMI at the screening visit (Visit 1), Visit 2, Visit 4, and Visit 5. Also, the subject's general condition including head, neck, heart, lung, abdomen, liver, skin, and extremities will be examined to check the health status and occurrence of any adverse events. Any significant change in physical examination will be reported as an AE.

8.3.8 Laboratory tests

Laboratory tests will be conducted to check the inclusion/exclusion criteria and assess the safety (Visit 1, Visit 4, Visit 5, Withdrawal visit, and Safety F/U). At Visit 1, a re-test may also be conducted once according to the investigator's judgment and, in such a case, evaluation will be based on the results of re-test. Hepatitis testing will be conducted at the screening visit (Visit 1) only.

① Hematology	WBC with differential count (neutrophil, lymphocyte, monocyte, eosinophil, basophil), RBC, hemoglobin, hematocrit, platelets
② Blood Chemistry	Random blood glucose, ureum, uric acid, AST, ALT, creatinine, total bilirubin
③ Blood Coagulation test	PT, INR, APTT
④ Urinalysis	pH, specific gravity, albumin, bilirubin, glucose, urobilinogen, ketone, nitrite, occult blood, microscopy (urine RBC, urine WBC)

Any clinically significant abnormalities before and after the IP administration will be recorded as medical history and AEs, respectively.

8.3.9 Pregnancy test

For women of childbearing potential, a pregnancy test with serum test or urine test will be conducted at the screening visit (Visit 1). If Visit 1 and Visit 2 are conducted on the same day, another pregnancy test (serum or urine test) will be conducted prior to IP administration even if the test result within 2 weeks before the date is available.

Women will be considered to be of non-childbearing potential if they:

① Have natural menopause (12 months of spontaneous amenorrhea; or follicle-stimulating hormone (FSH) >40 IU/L with 6 months of spontaneous amenorrhea)

② Are surgically sterile (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, etc.)

8.3.10 Inclusion/exclusion criteria

Enrollment will be decided when all screening results of the subjects who provided written consent are assessed collectively.

8.3.11 Re-screening

Patients who do not meet the criteria for participation in this study may be rescreened. Patients may be rescreened once, at the discretion of the investigator (or designee), providing that the reason for screen failure was not due to a safety concern. If a patient is considered eligible for rescreening, this will be discussed with the sponsor prior to rescreening. Patients who are rescreened will be identified by a new patient number.

8.3.12 Randomization

The subjects who are determined eligible for participation in this study for meeting the inclusion/exclusion criteria will be randomized in a 1:1 ratio to one of study group and control group.

The randomization number will be denoted by for example, '00RXXX (ex. 01R001)' and means the following.

- '00': means site number.
  - 01: RS. University of Indonesia
  - 02: RS. Islam Cempaka Putih
  - 03: RS. MMA
- 'R': means randomization
- 'XXX': order of randomized subjects

8.3.13 Investigational product administration

For maximum 8 weeks from the next day of investigational product dispensing, 1 tablet/capsule will be administered orally once daily without regard to meals. Tablets/Capsules should be taken at a regular time, if possible. At each visit after the administration of the IP all subjects should return the unused IP prescribed at the previous visit and empty packaging.

8.3.14 Distribution and Collection of Subject Diary

The subject diary will be distributed at Visit 2 and the training on how to complete it will be provided. The completion status of the subject diary will be checked at Visit 3 via site visit, and appropriate training on the diary keeping will be performed, if necessary. At Visit 4, the completed subject diary will be collected and the subjects who have not symptoms relief will be prescribed the IP for Treatment 2 and the subject diary will be re-distributed to the subject. At Visit 5, the subject diary will be collected only from those who have undergone Treatment 2. Assessment of symptoms and treatment compliance will be done based on the subject diary

8.3.15 Adverse events

All adverse events occurring from administration of the IP until the end will be collected.

8.4 Efficacy Assessment

8.4.1 Efficacy Endpoints

8.4.1.1 Primary Efficacy Endpoint

Proportions of subjects with symptoms relief at week 4 measured by GERD-Q Score <8

8.4.1.2 Secondary Efficacy Endpoints

1. Proportions of subjects with symptoms relief at week 8 measured by GERD-Q Score <8
   (Week 8 evaluation will only be applicable to patient receiving treatment 2)
2. Assessment on symptoms based on the diary of subjects
   - The day to reach complete response (disappearance of heartburn, acid regurgitation, or heartburn/acid regurgitation for 7 consecutive days) after the first IP administration.
   - Proportions of subjects without the major symptoms (heartburn, acid regurgitation, or heartburn/acid regurgitation) for first 7 days, 4 weeks, and 8 weeks after the first IP administration.
   - Proportions of days free of major symptoms (heartburn, acid regurgitation, or heartburn/acid regurgitation) for first 7 days, 4weeks, and 8 weeks after the first IP administration (including all daytime, nighttime, and daytime/nighttime)
   - However, the secondary efficacy endpoints will only be assessed in patients who are not healed with treatment 1 and will continue to receive safety and rescue.
     (Week 8 evaluation will only be applicable to patient receiving treatment 2)
3. Assessment on symptoms of reflux disease (GERD-Q)
   - Changes from baseline in frequency by major symptom after 7 days, 4 weeks and 8 weeks.
     (Week 8 evaluation will only be applicable to patient receiving treatment 2)
4. Assessment of Quality of Life (GERD-HRQL: GERD-Health related quality life)
   - Changes from baseline in the total score of GERD-HRQL after 7 days, 4 weeks and 8 weeks.
     (Week 8 evaluation will only be applicable to patient receiving treatment 2)

8.4.1.3 Exploratory Endpoints

Assessment on symptoms based on the diary of subjects.

- Proportions of subjects who have not been awakened during sleep for heartburn or acid regurgitation for first 3 days, 7 days, 4 weeks, and 8 weeks (or based on the day Investigator's need) after the first IP administration.

- Proportions of subjects who have relieved from chronic cough for first 3 days, 7 days, 4 weeks, and 8 weeks (or based on the day Investigator's need) after the first IP administration daytime and nighttime.
- Proportions of subjects who have relieved from irritating feeling in the throat for full 3 days, 7 days, 4 weeks, and 8 weeks (or based on the day Investigator's need) after the first IP administration daytime and nighttime.
  (Week 8 evaluation will only be applicable to patient receiving treatment 2)

8.4.2 Method of Efficacy Assessment

8.4.2.1 Proportions of Subjects with Symptoms Relief

The proportions of subjects with symptoms relief at Week 4 after IP administration will be calculated. GERD symptoms relief is defined by GERD-Q Score <8

8.4.2.2 Assessment on symptoms based on the diary of subjects

The subjects will self-assess each symptom of 'heartburn' and 'acid regurgitation' (major symptoms of gastroesophageal reflux disease) twice daily (daytime/nighttime combined) in the subject diary which then will be collected and analyzed. In addition, the presence of 'chronic cough' and 'foreign body sensation in the throat' which are non-typical symptoms of gastroesophageal reflux disease will be assessed twice daily (daytime/nighttime combined), and any experience of awakening during sleep for heartburn or acid regurgitation will be collected.
The scale (0 to 4) for scores of assessing daytime/nighttime combined symptoms of 'heartburn' and 'acid regurgitation' is as follows:

Assessment on daytime symptoms		
0	None	No symptoms
1	Mild	Symptoms noticeable, but not bothersome
2	Moderate	A little bothersome and some limitations of daily activities
3	Severe	Symptoms noticeable for a lot of time and frequent limitations of daily activities
4	Very severe	Symptoms persistent and considerable limitations of daily activities

Assessment on nighttime symptoms		
0	None	No symptoms
1	Mild	Symptoms noticeable, but can be ignored, and do not disturb sleep
2	Moderate	A little bothersome and some disturbance of sleep
3	Severe	Symptoms noticeable for a lot of time and frequent disturbance of sleep
4	Very severe	Symptoms persistent and difficulties in sleeping

8.4.2.3 Quality of Life assessment (GERD-HRQL)

The subjects will self-assess their symptoms on the GERD-HRQL assessment sheet which then will be collected and analyzed. The subjects will rate from 0 to 5 for each question.

0	No symptoms
1	Symptoms noticeable, but not bothersome
2	Symptoms noticeable and bothersome, but not every day
3	Symptoms bothersome everyday
4	Symptoms affect daily activities
5	Symptoms are incapacitating to do daily activities

- **Total Score: Calculated by summing the individual scores to questions 1-15.**
  - Greatest possible score (worst symptoms) = 75
  - Lowest possible score (no symptoms) = 0

8.5 Safety Assessment

8.5.1 Safety Endpoints

1. Adverse events
2. Vital signs (blood pressure [diastolic/systolic], pulse rate, and body temperature)
3. Physical examination (head to toe general physical examination)
4. Laboratory tests (hematology, blood chemistry, blood coagulation, urinalysis, Liver function, Renal Function)

8.5.2 Adverse events

8.5.2.1 Definition of Adverse Events

An ‘adverse event (AE)’ is defined as any unfavorable and unintended sign (including abnormal laboratory test results), symptom or disease in a subject who received the IP and which does not necessarily have to have a causal relationship with this IP.
An ‘adverse drug reaction (ADR)’ is defined as any untoward and unintended response to the IP of any dose, of which causal relationship to the IP cannot be excluded.
A ‘serious adverse event (SAE)’ is defined as an untoward medical occurrence that at any dose of IP meets one or more of the following criteria.

- Results in death or is life-threatening
- Requires or prolongs hospitalization
- Causes permanent or significant disability or incapacity
- Results in congenital anomalies or defect
- Besides events above, occurrence of other medically important events such as drug dependence, drug abuse, or blood dyscrasias

However, the following hospitalization scenarios are not considered to be SAEs:

- Hospitalization/surgery scheduled prior to study participation
- For emergency room visit, ≤24-hour stay in the emergency room (i.e., admission for >24 hours is considered as an SAE)
- Hospitalization or prolongation of hospitalization for elective surgeries for diagnoses or existing diseases
- Hospitalization for purposes other than improvement/treatment of poor health conditions (e.g., respite care, caregiver on leave, administrative reason)

An ‘unexpected adverse drug reaction’ is one for which the nature or severity of the reaction is not consistent with the available product-related information including the Investigator’s Brochure.

8.5.2.2 Criteria and Method for Adverse Event Assessment

Confirmed information such as occurrence of adverse event (AE), AE term, severity of AE, date of onset and resolution, relationship to the investigational product, action taken, treatment, and outcome will be recorded on the case report form.
Any laboratory abnormality and abnormal finding in physical examination or vital signs that are considered clinically significant will be recorded as AEs.

Adverse event (AE) from the first IP administration to safety follow up visit (visit 4-1 or 5-1) must be recorded regardless of its relationship with the IP. At each visit after IP administration, the following methods may be done to identify AEs:

- Information provided by subject or legal guardian without any prompt
- At each visit, asking open-ended and non-suggestive questions
- Abnormalities observed by the investigator, other medical professionals and relatives.

Except for lost to follow-up, AEs (including AEs unresolved until the completion of the study) will be monitored, if possible, until the AEs recover to the pre-dose state or to the baseline, or the investigator determines that the AEs have normalized or further monitoring is unnecessary.

8.5.2.2.1 Severity of Adverse Events

The severity of adverse events (AEs) should be evaluated according to the following criteria.

1) Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with normal daily activities (functions).
2) Moderate: An event that is sufficiently discomforting to interfere with normal daily activities (functions).
3) Severe: An event that prevents normal daily activities (functions).

8.5.2.2.2 Relationship to the Investigational Product

The investigator will determine the relationship between the adverse event (AE) and the IP in terms of subject's past history, health condition, treatment duration and treatment status.
1) Related: related or possibly related.
   A) Certain
      - The temporal sequence between the IP administration and the onset of the AE is reasonable.
      - The AE is most plausibly explained by the administration of the product than any other causes.
      - The AE disappears upon dechallenge.
      - The result of rechallenge (performed if practically feasible) is positive.

- The AE shows a pattern consistent with the known information about the IP or other same-class drugs.

B) Probable/Likely
- There is evidence of the IP administration.
- The temporal sequence between the administration of the product and the onset of the AE is reasonable.
- The AE is more plausibly explained by the administration of the product than any other causes.
- The AE disappears upon dechallenge.

C) Possible
- There is evidence of the administration of the product.
- The AE follows a reasonable temporal sequence from the time of administration of the product.
- The AE is considered to have been caused by administration of the product, as much as by other possible causes.
- The AE disappears upon dechallenge (if performed).

D) Un-assessable
- There is some information available about the AE, but the relationship to the product cannot be assessed.

2) Unrelated (None): probably or definitely not related.
- The subject has not received the product, or
- The AE does not follow a reasonable temporal sequence from the time of administration of the product, or
- Other evident causes (use of other drugs, latent diseases, other factors, etc.) can provide a reasonable explanation for the AE

8.5.2.2.3 Action Taken for Investigational Product

1) Dose not changed
2) Dose interrupted
3) Permanently discontinued
4) Not applicable
5) Unknown

8.5.2.2.4 Treatments Provided for Adverse Events

1) Medication treatment performed for the adverse event
2) Non-medication treatment performed for the adverse event
3) Medication/non-medication treatment performed for the adverse event
4) Medication/non-medication treatment not performed for the adverse event

8.5.2.2.5 Outcome of Adverse Events

1) Recovered/Resolved
2) Recovering/Resolving
3) Not recovered/Not resolved
4) Recovered/Resolved with Sequelae
5) Death
6) Unknown

8.5.2.3 Handling and Compensation of Adverse Events

If AEs are experienced by subject, they should be reported to the Investigator. Addressing any adverse events or discomfort related to the study and providing appropriate treatment will be done by the Investigator. The Investigator will also remain vigilant about these adverse events. If severe adverse events are experienced, the Investigator may need to discontinue the treatment. The subjects will be informed of the best approach to manage adverse events.

Except for lost to follow-up, AEs (including AEs unresolved until the completion of the study) will be monitored, if possible, until the AEs recover to the pre-dose state or to the baseline, or the investigator determines that the AEs have normalized or further monitoring is unnecessary.

This study has been insured. The costs of medical treatment or reasonable compensation for research-related injuries resulting from adverse events in the study are provided by the sponsor in accordance with applicable local laws. Compensation will follow the sponsor's compensation guidelines. Costs covered by the subject's personal health insurance

will not be reimbursed by the sponsor.

8.5.2.4 Obligations and Reporting Methods of Responsible Person in Case of Serious Adverse Events

During the study, the principal investigator and the sub-investigator should ensure the safety of subjects and take actions quickly and appropriately to minimize adverse events. If "serious adverse drug reactions" occur during the study, the obligation and reporting method of each responsible person are as below.

1) Principal Investigator

In the event of any serious adverse event (SAE) during the study, the principal investigator should promptly contact to the sponsor and the CRO (the responsible monitor) via telephone or email within 24 hours of awareness and for any initial/ follow-up SAE report the principal investigator should report within 3 calendar days to the IRB/EC. However, unexpected serious adverse drug reactions should be promptly reported to the sponsor and the IRB. In the event of reporting a death case, the principal investigator should provide additional information such as an autopsy report (only when performing an autopsy) and a death certificate to the sponsor and the IRB. The principal investigator should fully cooperate in providing the data and information of the report.

2) Sub-Investigators

Sub-investigators should report to the principal investigator and sponsor as soon as an SAE occurs during the study and make a further report on the details at a later time. However, unexpected serious adverse drug reactions should be promptly reported to the sponsor and the IRB.

3) Institutional Review Board/Ethical Committee

The Institutional Review Board (IRB)/Ethical Committee (EC) will ask the principal investigator to take necessary actions when any unexpected serious adverse drug reaction occurs or any new information that may adversely affect the safety of subjects or the conduct of the study becomes available.

4) Sponsor

The sponsor should periodically report additional safety information regarding the above report until the end of the AE (disappearance of the ADR or lost to follow-up) to the IRB/EC and/ or Indonesian Drug and Food Authority (BPOM) directly or through the CRO.

Safety Reporting Contact (within 24 hours of awareness)

TO CRO:

Telephone	(+62 21) 751-5932
E-mail	aufa.annisa@equilab-int.com

TO SPONSOR:

Email 1	ari_syam@hotmail.com
E-mail 2	pvsafety@daewoong.co.kr

8.5.3 Laboratory Tests, Vital Signs, Physical Examination

Results of the laboratory tests, vital signs, physical examination, will be evaluated for changes between before and after the IP administration and changes in normality/abnormality. Any clinically significant change will be recorded as an adverse event on the case report form.

8.5.4 Pregnancy

The subjects should use adequate methods of contraception during the study (Contraception should be maintained for at least 2 weeks from the last dose of IP). In this study, acceptable adequate methods of contraception for subjects or their partners:

- For Male subject: to use barrier method such as male condom and surgical sterilization such as vasectomy;

- For Female subject: to use 1) hormonal contraceptive such as Intraurine system : intrauterine hormone-containing system, implant, injection, contraceptive pills, or 2) non hormonal contraceptive such as Intraurine system : copper loop, barrier method : female condom, diaphragm or cervical cap, or surgical strerilization : tubectomy.

Female subject who became pregnant after enrolled to the study will be withdrawn from the study. The sponsor has the responsibility to follow up the outcome of the pregnancy in a female subject and male subjects' spouse (or partner) reported during the study. The information will be collected from the female subject and spouse (or partner) of male subject who have given a written consent to the informed consent form for collection of pregnancy information at the time the pregnancy is confirmed. Pregnancy itself will not be regarded as an adverse event unless the IP is suspected to have interfered with adequate methods of contraception or effects of contraceptives. Also, voluntary induced abortion without complications that is not a therapeutic abortion will not be considered as an adverse event and hospitalization for natural childbirth of a healthy baby will not be regarded as a serious adverse event.

Although pregnancy is not classified as a serious adverse event, the investigator should prepare a pregnancy report and report to the sponsor in the same way as serious adverse event reporting procedures in Section 8.5.2.4 within 24 hours of becoming aware of the pregnancy in a female subject or spouse (or partner) of a male subject. The investigator should follow and document the process and outcome of all pregnancy, even if the subject withdraws consent or terminates the study. Also, the investigator should prepare a pregnancy outcome report and report to the sponsor within 24 hours of becoming aware of any pregnancy outcomes (e.g., natural childbirth, spontaneous abortion). The follow-up of up to 7 days after delivery should be reported.

If an AE occurring during pregnancy meets the criteria for SAE (e.g., severe maternal complication, premature birth, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect), it should be immediately reported to the sponsor according to serious adverse event reporting procedures in Section 8.5.2.4.

9 Data Analysis and Statistical Considerations

9.1 Analysis Sets

Per Protocol Set (PPS)

The PPS will include the subjects in the FAS who complete the study without any major protocol deviation.
Major protocol deviations include 'violation of the inclusion and exclusion criteria', 'administration of prohibited concomitant medications during the study', etc. (see Section “13.5 Protocol Deviations”), and the subjects with other major deviations will be determined at the case report adjudication meeting prior to disclosure of randomization codes.

Full Analysis Set (FAS)

The FAS will include the subjects who receive the IP at least once after randomization and who have at least one efficacy assessment result. The subjects who violate the inclusion/exclusion criteria will be excluded from the FAS.
For the efficacy analysis, they will be included in the randomized treatment group regardless of the actual IP taken.

Safety Set

The safety set will include all the subjects who receive the IP at least once after randomization. The subjects who are enrolled in the study but withdrawn from the study before IP administration will be excluded from the safety set. For the safety analysis, the subjects will be analyzed according to the treatment they actually received.

9.2 Statistical Analysis Method

9.2.1 General Principles of Result Analysis

The efficacy analysis will be conducted primarily on the PPS and FAS, and the PPS will be the primary analysis set.
In principle, all statistical analyses will use SAS® version 9.4 or higher and be performed with a two-sided test at a significance level of 5%, unless otherwise specified.
Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be calculated and provided for continuous variables, and the frequency and percentage will be provided for categorical variables.
The last observation carried forward (LOCF) method will be applied for correction of missing data of continuous endpoints among efficacy endpoints, and if the LOCF method cannot be applied, the raw data will be analyzed without correcting the missing data. However, the quality-of-life score (GERD-HRQL) will be analyzed using the raw data without applying the LOCF. For survival analysis, censoring will be utilized. When applying the LOCF, if the value immediately before the missing value is the baseline value, it will not be replaced.
The missing values of efficacy endpoints will be handled for both analyses on the FAS and PPS, and the safety endpoints will be analyzed with the raw data without replacing the missing values.

9.2.2 Demographic Information and Clinical History

Background and demographic data of all subjects included in this clinical study will be assessed by group. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables (age, height, weight, BMI, etc.) and the frequency and percentage will be provided for categorical variables (gender, medical history, etc.).
To compare the difference between the groups, the two-sample t-test or the Wilcoxon rank sum test will be carried out for continuous variables, and Chi-square test or Fisher’s exact test will be carried out for categorical variables.

9.2.3 Efficacy Endpoints

9.2.3.1 Primary Efficacy Assessment

Proportions of subjects with symptoms relief at Week 4

The proportions of subjects with symptoms relief by Week 4 and their 95% confidence intervals will be provided by group.

The proportions of subjects with symptoms relief by Week 4 will be calculated as the cumulative symptoms relief by using the results at the time of final observation including the Withdrawal visit. To compare the control group and study group, the lower bound of the 2-sided 95% confidence intervals will be obtained by using Chi Square test or Fisher's Exact test method. If this lower bound is greater than the non-inferiority margin of -0.1, the study group will be judged to be non-inferior to the control group.

9.2.3.2 Secondary Efficacy Assessment

1. Proportions of subjects with symptoms relief at week 8 measured by GERD-Q Score <8

The proportions of subjects with symptoms relief by Week 8 and their 95% confidence intervals will be provided by group. The proportions of subjects with symptoms relief by Week 8 will be calculated as the cumulative symptoms relief by using the results at the time of final observation including the Withdrawal visit. To compare the control group and study group, the lower bound of the 2-sided 95% confidence intervals will be obtained by using the Chi Square test or Fisher's Exact test method. If this lower bound is greater than the non-inferiority margin of -0.1, the study group will be judged to be non-inferior to the control group. (Week 8 evaluation will only be applicable to patient receiving treatment 2)

2. Assessment on symptoms based on the diary of subjects

- CR (disappearance of heartburn, acid regurgitation, or heartburn/acid regurgitation for 7 consecutive days) is defined as the symptom score of 0 for 7 consecutive days for the first time after the first dose, and the survival time is defined as the time to reach Complete Response (CR) after the first IP administration. Kaplan-Meier plots will be drawn by treatment group, and the medians and their 2-sided 95% confidence intervals will be presented. To compare the control group and study group, the log-rank test will be used.
- The number of subjects without any heartburn, acid regurgitation, or heartburn/acid regurgitation for the first 7 days, full 4 weeks, and full 8 weeks from the first IP administration, the proportion (%) of these subjects and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Chi Square test or Fisher's Exact test method.
- Descriptive statistics (mean, standard deviation, median, minimum, and maximum) of the proportions of days free of any heartburn, acid regurgitation, or heartburn/acid regurgitation for the first 7 days, full 4 weeks, and full 8 weeks from the first IP administration will be presented for daytime, nighttime, and daytime/nighttime by group. For comparison between treatment groups, an ANCOVA model will be applied with treatment group as a treatment effect. The results of ANCOVA model will be summarized as the LSM differences between the study group and the control group, the corresponding 2-sided 95% confidence interval, and p-value.
  (Week 8 evaluation will only be applicable to patient receiving treatment 2)

3. Assessment on symptoms of reflux disease using GERD-Q

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for the changes from baseline in frequency at the first 7 days, 4 weeks, and 8 weeks will be presented by time point. For the changes from baseline in variables measured at the first 7 days, 4 weeks, and 8 weeks after the IP administration, an ANCOVA model including treatment group as treatment effect, and baseline value will be applied. The results of ANCOVA model will be summarized as the least squares mean (LSM) and standard error by treatment group, the LSM differences between the study group and the control group, the corresponding 2-sided 95% confidence interval, and p-value
(Week 8 evaluation will only be applicable to patient receiving treatment 2)

4. Quality of life assessment using GERD-HRQL

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for the changes from baseline in the total score of quality of life at the first 7 days, 4 weeks, and 8 weeks will be presented by time point. For the changes from baseline in variables measured at the first 7 days, 4 weeks, and 8 weeks after the IP administration, an ANCOVA model including treatment group as treatment effect, baseline values, and stratification factor (based on dominant symptoms in inclusion criteria: experiencing heartburn, regurgitation, or both of them more than >3 days in the last 7 days) as covariate will be applied. The results of ANCOVA model will be summarized as the least squares mean (LSM) and standard error by treatment group, the LSM differences between the study group and the control group, the corresponding 2-sided 95% confidence interval, and p-value. (Week 8 evaluation will only be applicable to patient receiving treatment 2)

9.2.3.3 Exploratory Endpoints

Assessment on symptoms based on the diary of subjects.

- The proportions (%) of subjects who have not been awakened during sleep for heartburn or acid regurgitation for the first 7 days, full 4 weeks, and full 8 weeks after the first IP administration and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Cochran-Mantel-Haenszel method.
- The proportions (%) of subjects who have relieved from chronic cough for the first 7 days, full 4 weeks, and full 8

weeks after the first IP administration and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Chi Square test or Fisher's Exact test method.

- The proportions (%) of subjects who have relieved from foreign body sensation for the first 7 days, full 4 weeks, and full 8 weeks after the first IP administration and its 95% confidence interval will be presented by treatment group. To compare the control group and study group, the 2-sided 95% confidence intervals and p-value will be obtained by using the Chi Square test or Fisher's Exact test method.
  (Week 8 evaluation will only be applicable to patient receiving treatment 2)

9.2.4 Safety Endpoints

Safety analysis will be conducted using the safety sets, based on AEs, vital sign abnormalities, laboratory abnormalities, physical examination abnormalities, etc.

9.2.4.1 Adverse events

AEs will be recorded based on worsening of existing symptoms or the newly occurring treatment-emergent adverse events (TEAEs) after administration of the IP.
For TEAEs, adverse drug reactions (ADRs), and serious adverse events (SAEs), descriptive statistics (number of subjects, incidence (%), and number of cases) will be presented, and Chi-square test or Fisher's exact test will be used for analysis depending on whether cells with the expected frequency of <5 is >20% or not.
AEs, ADRs, and SAEs will be coded by system organ class (SOC) and preferred term (PT) using the medical dictionary for regulatory activities (MedDRA) version 21.0 (or higher), and coded AEs will be presented with the number of subjects, incidence, and the number of cases by treatment group. The frequency and percentage of subjects who are withdrawn due to serious adverse events or AEs will be presented and the listings will be provided.

9.2.4.2 Laboratory Tests, Vital Signs, and Physical Examination

The descriptive statistics (mean, standard deviation, median, minimum, maximum, etc.) will be presented for continuous data, such as hematology, blood chemistry results, and vital signs by treatment group and visit; the frequency and percentage will be presented for categorical data, such as urinalysis, physical examination by category.
For continuous variables, the paired t-test or Wilcoxon signed-rank test for intra-group tests for the difference between Predose (Visit 2 or Visit 1 if there is no Visit 2) and post dose will be conducted to compare the inter-visit differences. The two-sample t-test and Wilcoxon rank sum test will be carried out to compare the difference between the study group and the control group in the changes before and after administration.
For the categorical variables, the McNemar's test will be conducted for the intra-group change (Normal/NCS vs CS), and the Chi-square test or Fisher's exact test will be conducted for the inter-group difference.

9.3 Criteria

Hypothesis: The study group (Fexuprazan 40 mg) is non-inferior to the control group (Esomeprazole 40 mg) in terms of the proportions of subjects with symptoms relief by Week 4.
To determine the noninferiority of the study group (Fexuprazan 40 mg) against the control group (Esomeprazole 40 mg), the Chi Square test or Fisher's Exact test method will be used. The lower limit of the 2-sided 95% confidence intervals for the difference between the study group and control group (study group minus control group) will be calculated, and if this lower limit is larger than the non-inferiority margin of -0.1, the study group will be declared non-inferior to the control group.

9.4 Time of Analysis and Rationale for Determination of Sample Size

9.4.1 Time of Analysis

Interim analysis is not planned for this study, and the analysis will be started after the study ends.

9.4.2 Rationale for Determination of Sample Size

This study objective is to determine the non-inferiority of the study group (Fexuprazan 40 mg) compared to the control group (Esomeprazole 40 mg) in patients with erosive gastroesophageal reflux disease. The primary endpoint is the proportions of subjects with symptoms relief at week 4 measured by GERD-Q Score <8, and the hypothesis is:

$$H_0: \pi_T - \pi_C \leq -0.1 \qquad \text{vs.} \qquad H_A: \pi_T - \pi_C > -0.1$$

π_T: Proportion of subjects with symptoms relief at week 4 (measured by GERD-Q score <8) in the study group (Fexuprazan 40 mg)
π_C : Proportion of subjects with symptoms relief at week 4 (measured by GERD-Q score <8) in the control group (Esomeprazole 40 mg)

The proportion of subjects with symptoms relief at week 4 of proton pump inhibitors (PPI) was considered to be 88.5%, and this value was set as the proportion of symptoms relief for the control group (Esomeprazole 40 mg). In this study, the proportion of symptoms relief of the study drug was assumed to be higher than control drug, therefore, 94.0% was set as the proportion of symptoms relief in the study group.
The number of subjects calculated by "Non-Inferiority Tests for the Difference Between Two Proportions" of PASS2020 with the non-inferiority margin of -0.1, the one-sided significance level of 2.5%, 80% statistical power, and 1:1 randomization allocation, was 53 per group. And considering a dropout rate of 20%, a total of 134 subjects will be enrolled in the study.

Non-Inferiority Tests for the Difference Between Two Proportions

Numeric Results

Test Statistic: Z-Test with Pooled Variance
Hypotheses: H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 > D0

Target Power	Actual Power*	N1	N2	N	Ref. P2	P1|H0 P1.0	P1|H1 P1.1	NI Diff D0	Diff D1	Alpha
0.80	0.80729	53	53	106	0.8850	0.7850	0.9400	-0.1000	0.0550	0.025

* Power was computed using the normal approximation method.

10 Data Management (Recording, Collection, Access, Protection, and Storage)

10.1 Data Recording

1) The investigator or the person authorized by the investigator should record all data collected in the study on the electronic case report form provided by the sponsor.
2) The investigator should record a reasonable explanation for missing data.
3) Recorded case report form will be finally signed by the principal investigator.

10.2 Data Collection

The protocol-required data will be collected via the electronic case report form (e-CRF), and all information recorded on the CRF must be consistent with the source document (SD).
Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines.
The investigator has ultimate responsibility for the collection and recording of all clinical data to be entered on the CRF. After completing the CRF, the investigator will assure that information recorded on the CRF is true by signing each CRF. In all cases, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRF.

10.3 Data Access

The sponsor should establish a security system to prevent unauthorized access. Also, the list of persons authorized to modify the data should be prepared. Since this study is a collaborative study between the sponsor and Daewoong Pharmaceutical Co.,Ltd, a pharmaceutical company located in South Korea, the completed original copy of the CRF is the sole property of Prof. Dr. dr. Ari Fahrial Syam, SpPD, K-GEH, MMB, FACP, FACG, FINASIM. The original copy of the CRF and other data cannot be disclosed to any third parties without written permission of the sponsor.

10.4 Protection and Storage of Data

The sponsor and investigator are responsible for retaining clinical study data even after the study completion or termination, and it is mandatory to retain the related clinical documents for at least 3 years since the date of study.
The retention period may be extended if ordered by the Indonesian Food and Drug Authority or determined necessary by the local authorization. The sponsor should inform the investigator and the head of study site about the necessity and duration of data retention in writing. If the sponsor determines that data retention is no longer necessary, they should also inform the principal investigator and the head of study site in writing.

If the PI retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the study center or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian before such transfer is made.
No study records shall be destroyed without notifying and giving the Sponsor the opportunity to arrange long-term storage for such study records or to authorize in writing the destruction of records after the required retention period.

11 Ethical considerations and Administrative Procedures

11.1 Indonesian Good Clinical Practice (CUKB) and Declaration of Helsinki

These protocol-specified procedures are prepared in compliance with international council for harmonization (ICH) good clinical practice (GCP), Indonesian good clinical practice and basic principles of the Declaration of Helsinki for the study sponsor and the investigators to conduct and assess the study and record its result. This study will also be conducted in compliance with national applicable regulations.

11.2 Informed Consent

1) The investigator should provide the subjects (or their legally acceptable representative) with detailed explanation of all information about the study and ample opportunities to know all foreseeable outcomes.
2) The investigator should provide the subjects with sufficient time to decide whether to participate in this study. Once explanation is provided, the subjects should make their decision in an independent area without the presence of investigators or sub-investigators and should be recommended to make the decision at their next visit, if possible.
3) Subject informed consent must be documented. By signing the consent form, the subject agrees to participate in the study and to the collection and use of the subject's personal information in association with the study. The subject's personal information will be used to identify the subject and linked to the clinical data collected during the study. Collected personal information will be coded to avoid identifying individuals and will not be used directly as study data.
4) The investigator should confirm by signing the informed consent form. The investigator should not perform any protocol-specific tests before obtaining informed consent from the subjects.
5) For vulnerable subjects, the investigator should use an additional informed consent form and obtain consent from them according to the procedures 1) to 4).

11.3 Measures to Protect the Safety of Vulnerable Subjects

"Vulnerable subjects" refers to the subjects whose voluntary decision to participate may be affected by the expectation of benefits associated with the study participation or a concern about possible disadvantage received from senior members of an organizational hierarchy in case of refusal to participate (e.g., a student at college of medicine, Indonesian medicine, pharmacy, dentistry, or nursing, employee of medical institution or research laboratory, employee of pharmaceutical company, soldier, etc.), patients with incurable disease, persons in a collective facility per Article 27 of ‘Regulation on the Safety of Pharmaceuticals, etc.’, unemployed, poor, patients present in an emergency condition, ethnic minorities, vagrants, homeless, refugees, minors, or subjects who cannot freely give consent.

If employees of the study site, investigator or sponsor, students, etc. wish to participate in the study, their participation in this study will not be limited in order to prevent reverse discrimination against them. The number of vulnerable subjects should not exceed 20% of the total number of subjects. The following should be complied with when recruiting vulnerable subjects.

1) The investigators should not interact directly with the employees or students for the purpose of subject recruitment and should not recruit any subjects or conduct the study during work or class.
2) Recruitment for the study or informed consent process should be conducted in the absence of senior members of employees or students, if possible.
3) Employees or students can decide not to participate in the study, and they should be informed that such decision will not affect their employment, job or grading.
4) It should be guaranteed that employees or students will not be unduly influenced or forced and that their privacy will be respected.
5) Measures should be taken to ensure that the employee's or student's refusal to participate in the study is not disclosed to their senior members.
6) The study should be conducted in the absence of other employees or students, if possible.
7) If an employee of the sponsor is recruited as a subject, the identity of the employee should be protected by summarizing all data to be provided to the sponsor, or by removing any personally identifiable information.

11.4 Ethical Compliance

The study should be conducted in compliance with the protocol (including subject information sheet and informed consent form) approved by the institutional review board (IRB) and Badan Pengawas Obat dan Makanan (BPOM). The study should be also conducted in compliance with Indonesian good clinical practice (CUKB) and basic principles of the Declaration of Helsinki.

11.5 Measures to Protect the Safety of Subjects

All investigators and sub-investigators will be thoroughly familiarized with the protocol and conduct the study in accordance with the protocol. The principal investigator must take prior measures, including countermeasures against unexpected

adverse events, etc. and required reports as well as sufficient training for sub-investigators.

11.6 Utilization and Publication of Study Results

By signing the study protocol, the sub-investigators agree that the results of the study may be used for the purposes of registration, publication, and information for medical and pharmaceutical professionals. The sponsor has the right to review the contents prior to publication of this study results in scientific congresses or journals.

11.7 Subject Confidentiality

Names of subjects will remain confidential, and subjects will be identified by the identification codes (screening numbers) for recording and assessment. The subjects will be informed that all study data will be stored on the computer and treated with strict confidentiality. The signed informed consent form will be retained by the principal investigator. The principal investigator should make a list of subject identification codes (screening numbers) and names and keep relevant records. The informed consent form and subject list will be retained for at least 3 years from the date of study completion or marketing approval.

11.8 Quality Control and Reliability Assurance

Monitoring will be performed to protect the right and welfare of subjects, to check the accuracy, completeness and verifiability of the reported study-related data in comparison with source documents, and to check whether the study is conducted in accordance with the approved protocol, Indonesian GCP and applicable regulations.

The sponsor (or sponsor's designee) or the monitor will monitor the study through regular site visits and contacts. The visit schedule will be settled in proper consultation between the investigator and the monitor.

The monitor will visit the study site to check the completeness and clarity of the entries on the CRF, compare them with source data, and check administrative duties, and the investigator should cooperate with them. During the monitoring visit, the monitor will review the informed consent form, patient recruitment and follow-up, records and reports of SAEs, IP assignments, patient's compliance with the dose and regimen of the IP, the quantity of IPs, concomitant treatments, and data quality, with the investigators.

In order to guarantee the reliability during the study, the sponsor may perform audits, in addition to the general monitoring. An audit will include checking on whether this study is conducted in compliance with the protocol, standard operating procedure, and applicable regulations including the Indonesian GCP, and review of all source data, drug records, medical records, etc. The sponsor (or sponsor's designee) may require access to the source documents and other essential documents for the audit of the study site, and the investigators should allow such access and cooperate in the process.

Regulatory authorities may perform inspection at any time during the study or at the end of the study. In the event of audit or inspection, the investigators (and sites) will allow the auditor and inspector direct access to relevant data, and agree to allocate time of investigators themselves or other personnel, and to cooperate for discussion of issues found or related matters.

11.9 Protocol Approval

The study can be initiated after the protocol and other related documents are submitted to and approved by the Indonesian Food and Drug Authority (BPOM) and the IRB.

11.10 Protocol Amendment

Neither the principal investigator nor the sponsor can modify the contents of the protocol during the course of the study without the consent of the other. Once the study is initiated, amendment can be made only in exceptional cases. To modify the protocol, all involved parties must provide written consent by signature. In order to amend the approved study, the approval of the IRB should be obtained for the amended protocol and if necessary, an approval from the Minister of Food and Drug Safety should be obtained.

12 Sponsor Information, and Name and Title of Principal Investigator

12.1 Study Sponsor

Prof. Dr. dr. Ari Fahrial Syam, SpPD, K-GEH, MMB, FACP, FACG, FINASIM with collaborative partner Daewoong Pharmaceutical, Co. Ltd.

12.2 Name and Title of Principal Investigator

Refer to Appendix 1. List of Study Sites and Principal Investigators

13 Other Matters Required to Conduct the Study Safely and Scientifically

13.1 Study Site

The head of a study site should fully prepare study facilities and specialized personnel needed for conducting the study for each study phase and be ready for the proper conduct of the study.

13.2 Principal Investigator

The principal investigator will be fully familiar with the solicited adverse events and precautions in the protocol in advance, and immediately notify the Institutional Review Board and the sponsor of any serious adverse events, etc. during the study.

13.3 Sub-Investigators

The sub-investigators will be fully familiar with the solicited adverse events and precautions for use in the protocol in advance, and immediately notify the principal investigator and the sponsor of any serious adverse events, etc. during the study.

13.4 Understanding of Protocol

The principal investigator and sub-investigators should thoroughly understand the protocol, and then conduct the study.

13.5 Protocol Deviation

If any protocol deviation becomes known during the study, the investigator should notify the deviation to the sponsor as soon as possible and decide whether to continue participation of the subject in the study. The followings are regarded as major protocol deviations:

1) Violation of inclusion and exclusion criteria
2) Administration of prohibited concomitant medications/therapies that may affect the study results
3) Treatment compliance of <80% or >120%
   (Treatment compliance refers to the mean treatment compliance throughout the study treatment period for Fexuprazan 40 mg).
4) Other deviation considered as a major protocol deviation

For other minor deviations, the degree and reason of deviation or delay will be described accurately, and consideration on whether the study has been affected will be made at the time of result analysis.

13.6 Criteria for the Subject's Medical Care and Treatment after the Study

Subsequent medical care and treatment for subjects who terminate the study early or complete the study will be in accordance with general principle of medical care and treatment of a patient with gastroesophageal reflux disease.
However, if the subject is injured from the treatment or clinical procedure which would not have been performed if the subject has not participated in the study, he/she will receive every treatment according to the standard processes of the hospital. If the injury is related to the study, the cost will be covered in accordance with the participant compensation rule and the sponsor's insurance conditions of the study.

13.7 Independent Data Monitoring Committee

The study will not constitute a separate Independent Data Monitoring Committee (IDMC).

13.8 Expected Adverse Events Caused by the Investigational Product and Precautions for Use

13.8.1 Expected Adverse Events of Fexuprazan

The adverse events predicted from the results of phase 1 and phase 2 studies of Fexuprazan performed so far are as follows.

1) Phase 1 Study (DW_FEXUPRAZAN001)

A dose block-randomized, double-blind, placebo- and active-controlled, single and multiple dosing, dose-escalation clinical phase 1 trial to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of Fexuprazan after oral administration in healthy male volunteers was conducted. A total of 28 and 35 adverse events occurred in single and multiple dosing studies, receptively, and they were all mild in severity and recovered without any actions taken. Among them, the adverse drug reactions for which possible relationship to the FEXUPRAZAN cannot be ruled out are:

Study	Dose group	Adverse drug reaction term	Severity
Single Dosing Study	FEXUPRAZAN 20 mg	Epigastric discomfort Dyspepsia	Mild Mild
	FEXUPRAZAN 80 mg (fasting)	Headache	Mild
	FEXUPRAZAN 80 mg (fed)	Vomiting (2 events) Headache	Mild Mild
	FEXUPRAZAN 160 mg	Nausea	Mild

Multiple Dosing Study	FEXUPRAZAN 40 mg	Abdominal distension Abdominal pain Skin exfoliation Headache	Mild Mild Mild Mild
	FEXUPRAZAN 80 mg	Blood creatine phosphokinase increased Abdominal discomfort	Mild Mild

2) Phase 2 Study (DW_FEXUPRAZAN002)

A multi-center, randomized, double-blind, active-controlled, phase 2, therapeutic exploratory study was conducted to evaluate the efficacy and safety of Fexuprazan in patients with erosive gastroesophageal reflux disease. The result of safety assessment showed that 63 adverse events occurred in 36 out of 156 subjects who were treated with Fexuprazan, 24 events of which were adverse drug reactions occurring in 13 subjects. Among them, the adverse drug reactions for which possible relationship to the Fexuprazan cannot be ruled out are:

Dose group	Adverse drug reaction term	Severity
FEXUPRAZAN 20 mg	Nausea Abdominal pain Urticaria Oesophageal candidiasis	Mild Mild Mild Mild
FEXUPRAZAN 40 mg	Nausea Abdominal discomfort Headache Erythema Myalgia Feeling abnormal	Mild Mild Mild Mild Mild Mild
FEXUPRAZAN 80 mg	Headache Dizziness (2 events) Rash (2 events) Alanine aminotransferase increased (3 events) Aspartate aminotransferase increased (3 events) Blood lactate dehydrogenase increased Gamma-glutamyltransferase increased Myalgia	Mild Mild Mild Mild Mild Mild Mild Mild

14 Reporting and Publication

14.1 Clinical Study Report

The data and information collected during this study will be reported in a study report prepared by the CRO. Sponsor and Daewoong Pharmaceutical Co, Ltd will be provided the information regarding study product. The final report may be used for the further development of the investigational product as considered necessary by the Sponsor and/or Daewoong Pharmaceutical Co.,Ltd.

14.2 Confidentiality and Intellectual Property Rights of Study Data

Any confidential information relating to the investigational product or the study, including any data and results from the study will be the exclusive property of the Sponsor and Daewoong Pharmaceutical Co.,Ltd. The Investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to the Sponsor.

14.3 Publication Policy

The Sponsor encourages the publication of results derived from clinical research. Publications include a paper in a peer-reviewed medical journal, abstract submission with a poster or oral presentation at a scientific meeting or making results public by some other means. The Sponsor and Daewoong Pharmaceutical Co.,Ltd will retain the right to review all material prior to presentation or submission for publication and neither institution(s) nor Study Co-chairs/PI(s) are permitted to publish/present the results of the study, in part or in their entirety, without the written authorization of the Sponsor. The review is aimed at protecting the Sponsor's pre-existing proprietary information and commercial interests.

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15. Appendix

Attachment 1. List of Study Sites and Principal Investigators

No.	Site No.	Site Name	Investigator Name	Position
1	Site 01	RS. University of Indonesia	dr. M. Firhat Idrus, SpPD, K-GEH	Principal Investigator

2	Site 02	RS. Islam Cempaka Putih	Prof. Dr. dr. Ari Fahrial Syam, SpPD,K-GEH, MMB, FACP, FACG, FINASIM	Coordinating Investigator
3	Site 02	RS. Islam Cempaka Putih	dr. Ihsanil Husna, SpPD, FINASIM	Principal Investigator
4	Site 03	RS. MMA	dr. Dirga Sakti Rambe, SpPD, M.Sc,	Principal Investigator

Attachment 2. Gastroesophageal Reflux Disease Questionnaire (GERD-Q)

Screening No.	_ _ S _ _ _		Subject No.	_ _R _ _ _		
Subject initial						
Visit No.	☐ Visit 1	☐ Visit 2	☐ Visit 3	☐ Visit 4	☐ Visit 5	□ Early withdrawal or unscheduled visit

Cobalah mengingat apa yang Anda rasakan dalam 7 hari terakhir					
Berikan tanda centang (v) hanya pada satu tempat untuk setiap pertanyaan dan hitunglah poin GERD-Q Anda dengan menjumlahkan poin pada setiap pertanyaan.					
No.	**Pertanyaan**	**Frekuensi dari skor (poin) untuk gejala**			
		0 hari	**1 hari**	**2-3 hari**	**4-7 hari**
1.	Seberapa sering Anda mengalami perasaan terbakar di bagian belakang tulang dada Anda (*heartburn*)?	☐ 0	☐ 1	☐ 2	☐ 3
2.	Seberapa sering Anda mengalami naiknya isi lambung ke arah tenggorokan/mulut Anda (regurgitasi)?	☐ 0	☐ 1	☐ 2	☐ 3
3.	Seberapa sering Anda mengalami nyeri ulu hati?	☐ 3	☐ 2	☐ 1	☐ 0
4.	Seberapa sering Anda mengalami mual?	☐ 3	☐ 2	☐ 1	☐ 0
5.	Seberapa sering Anda mengalami kesulitan tidur malam oleh karena rasa terbakar di dada (*heartburn*) dan/atau naiknya isi perut?	☐ 0	☐ 1	☐ 2	☐ 3
6.	Seberapa sering Anda meminum obat tambahan untuk rasa terbakar di dada (*heartburn*) dan/atau naiknya isi perut (regurgitasi), selain yang diberikan oleh dokter Anda? (seperti obat maag yang dijual bebas)	☐ 0	☐ 1	☐ 2	☐ 3
Hasil		Bila poin GerdQ Anda ≤ **7**, kemungkinan Anda **tidak menderita GERD** Bila poin GerdQ Anda **8-18**, kemungkinan Anda **menderita GERD**			

*) The Gastroesophageal Reflux Disease Questionnaire has been validated by Marcellus Simadibrata, Aziz Rani, Pangestu Adi, Ali Djumhana, Murdani Abdullah with an article titled “The gastro-esophageal reflux disease questionnaire using Indonesian language: a language validation survey” at May 2011.

Documented date	Date	Month	Year 20	Documented by	(Signature)
Reviewed date	Date	Month	Year 20	Documented by	(Signature)

Attachment 3. Quality of Life Questionnaire (GERD-HRQL; GERD-Health Related Qualityof Life)

Screening No.	_ _ S _ _ _		Subject No.	_ _R _ _ _	
Subject initials					
Visit No.	□ Visit 2	□ Visit 3	□ Visit 4	□ Visit 5	□ Early withdrawal or unscheduled visit

Check each applicable item in the below check boxes.

0 poin	Tidak ada gejala
1 poin	Gejala terlihat tapi tidak mengganggu
2 poin	Gejala terlihat dan mengganggu tapi tidak setiap hari
3 poin	Gejala mengganggu setiap hari
4 poin	Gejala mempengaruhi aktivitas sehari-hari
5 poin	Gejala menyebabkan ketidakmampuan untuk melakukan aktivitas

For each question, what score best describes your symptoms?

1	Seberapa buruk rasa terbakar di dada Anda?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
2	Rasa terbakar di dada saat berbaring?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
3	Rasa terbakar di dada saat berdiri?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
4	Rasa terbakar di dada setelah makan?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
5	Apakah rasa terbakar di dada mengubah diet Anda?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
6	Apakah rasa terbakar di dada membuat Anda terbangun dari tidur?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
7	Apakah Anda mengalami kesulitan menelan	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
8	Apakah Anda memiliki perasaan kembung atau perasaan penuh dengan gas?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
9	Apakah Anda memiliki rasa sakit saat menelan?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
10	Jika Anda minum obat, apakah ini mempengaruhi kehidupan sehari-hari Anda?	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5
11	Seberapa puas anda dengan kondisi anda saat ini?	□ Satisfied		□ Average		□ Not satisfied	

***)** The GERD Health Related Quality of Life Questionnaire has been validated by Laura A. Siahaan, Ari F. Syam, Marcellus Simadibrata, Siti Setiati with an article titled “The Validity and Reability Test of the Indonesian version of Gastroesophageal Reflux Disease Quality of Life (GERD QOL) Questionnaire” at January 2017.

Documented date	Date	Month	Year 20	Documented by	(Signature)
Reviewed date	Date	Month	Year 20	Documented by	(Signature)

Attachment 4. Subject Diaries Ver 1.0 (2018/07/26)

BUKU HARIAN SUBJEK

VISIT (TANGGAL BUKU HARIAN DIBAGIKAN)	☐ Visit 2 ☐ Visit 3 ☐ Visit 4
TANGGAL VISIT	_ _ _ _ _ _ DD MM YY
NOMOR SUBJEK	_ _R _ _ _
INISIAL SUBJEK	
TANDA TANGAN SUBJEK	

Anda sedang berpartisipasi dalam uji klinis DWP14012 penyakit refluks gastroesofageal erosif (GERD). Buku harian subjek ini dirancang untuk menilai tingkat keparahan dan frekuensi gejala penyakit refluks gastroesofageal erosif Anda. Materi ini akan digunakan sebagai data untuk mengevaluasi efektivitas dan keamanan dari DWP14012, oleh karena itu, harap baca panduan berikut dengan cermat sebelum mencatat dan mengisi dengan teliti agar tidak melewatkan bagian apapun.

– Petunjuk Pengisian –

- ✓ Anda akan mengevaluasi gejala utama penyakit refluks gastroesofageal ① "heartburn" dan ② "refluks asam lambung", serta gejala atipikal ③ "batuk kronis" dan ④ "sensasi mengganggu di tenggorokan" dua kali sehari (siang/malam) dan mencatatnya dalam buku harian subjek. Selain itu, catat ⑤ 'apakah Anda terbangun selama tidur karena “heartburn” dan refluks asam lambung.

- ✓ **① “Heartburn”** didefinisikan sebagai ketidaknyamanan atau rasa panas atau nyeri seperti sensasi terbakar di dada.

- ✓ **② “Refluks asam lambung”** didefinisikan sebagai naiknya cairan asam atau pahit ke tenggorokan atau mulut, atau rasa asam dan pahit di mulut.

- ✓ **③ “Batuk kronis”** didefinisikan sebagai batuk kering yang menetap dan terus menerus, tanpa dahak dan iritasi atau gangguan pada tenggorokan disertai dengan naiknya cairan asam atau pahit dari lambung.

- ✓ **④ “Sensasi mengganggu di tenggorokan"** didefinisikan sebagai perasaan seolah ada sesuatu yang mengganjal di tenggorokan.

✓ Pada bagian “Siang hari” di buku harian, catat gejala yang Anda rasakan dalam satu hari sebelum tidur, sesuai kriteria di bawah

✓  Pada bagian “Malam hari” di buku harian, catat gejala yang Anda rasakan selama malam hari saat bangun di pagi hari berikutnya. Apabila Anda mengalami beberapa gejala. Tulislah gejala yang dirasa paling tidak nyaman dan menyakitkan.

✓ Gejala “Heartburn” dan “refluks asam lambung” dinilai berdasarkan skala 0 hingga 4, dengan kriteria sebagai berikut.

Penilaian gejala “siang hari” (waktu beraktivitas)		
0	Tidak ada	Tidak ada gejala
1	Ringan	Gejala dirasakan tetapi tidak ada rasa tidak nyaman
2	Sedang	Sedikit ketidaknyamanan dan sedikit keterbatasan dalam aktivitas normal sehari-hari
3	Berat	Gejala sering dirasakan, dan sering terjadi keterbatasan dalam aktivitas normal sehari-hari
4	Sangat Berat	Gejala yang terus menerus dan keterbatasan yang signifikan terhadap aktivitas normal sehari-hari

Penilaian gejala “malam hari” (waktu tidur)		
0	Tidak ada	Tidak ada gejala
1	Ringan	Gejalanya terasa, namun bisa diabaikan dan tidak mengganggu tidur
2	Sedang	Sedikit ketidaknyamanan, sedikit gangguan pada tidur
3	Berat	Gejalanya sering dirasakan, dan sering terjadi gangguan tidur
4	Sangat Berat	Gejalanya dirasakan terus menerus, dan sulit tidur

– Perhatian –

- ✓ Gunakan pulpen berwarna hitam jika memungkinkan, dan saat mengubah isi, coret area yang perlu diperbaiki dengan garis lurus, tulis perbaikannya, tanggal dilakukan perbaikan, alasan perbaikan, dan kemudian tandatangani. Harap gunakan tanda tangan yang sama dengan tanda tangan di sampul buku.

  Contoh) ~~LAR~~ LAK 16/04/2017, salah tulis, (tanda tangan)

- ✓ Obat penelitian harus diminum sekali sehari tanpa mempertimbangkan waktu makan dan sebaiknya diminum pada waktu yang tetap. Mohon cantumkan di buku harian subjek jika Anda sudah mengonsumsinya. Pada kunjungan berikutnya, Anda harus mengembalikan kotak obat, sisa obat yang belum digunakan, dan kemasan obat yang sudah kosong.
- ✓ Saat kunjungan berikutnya, pastikan untuk membawa formulir aplikasi Anda.
- ✓ Kami meminta kerjasama Anda dengan staf medis hingga akhir studi ini. Jika Anda mengalami ketidaknyamanan atau kejadian yang tidak diharapkah selama periode uji klinis, mohon beri tahu staf medis penelitian.

Peneliti atau perawat penelitian	Kontak

<table>
<tr><td colspan="4">Hari ke- ( ) Tanggal: Bulan: Tahun:</td></tr>
<tr><td colspan="4">Apakah Anda sudah mengonsumsi obat investigasi uji klinis? □ Ya □ Tidak</td></tr>
<tr><td colspan="2"> Siang hari (diisi sebelum tidur di malam hari)</td><td colspan="2">  Malam hari (diisi setelah bangun tidur di pagi hari)</td></tr>
<tr><td>Nyeri ulu hati</td><td>□ Tidak ada
□ Ringan
□ Sedang
□ Berat
□ Sangat berat</td><td>Nyeri ulu hati</td><td>□ Tidak ada
□ Ringan
□ Sedang
□ Berat
□ Sangat berat</td></tr>
<tr><td>Refluks asam lambung</td><td>□ Tidak ada
□ Ringan
□ Sedang
□ Berat
□ Sangat berat</td><td>Refluks asam lambung</td><td>□ Tidak ada
□ Ringan
□ Sedang
□ Berat
□ Sangat berat</td></tr>
<tr><td>Batuk kronis</td><td>☐ Tidak
☐ Ya</td><td>Batuk kronis</td><td>☐ Tidak
☐ Ya</td></tr>
<tr><td>Sensasi mengganggu di tenggorokan</td><td>☐ Tidak
☐ Ya</td><td>Sensasi mengganggu di tenggorokan</td><td>☐ Tidak
☐ Ya</td></tr>
<tr><td colspan="2"></td><td>Pernahkah Anda terbangun dari tidur karena gejala “nyeri ulu hati” atau “refluks asam lambung”?</td><td>☐ Tidak
☐ Ya</td></tr>
</table>

Memo

NO	TANGGAL	CATATAN