

**CLINICAL RESEARCH PROPOSAL****RESEARCH TITLE:****Effectiveness of Vonoprazan vs Omeprazole as Empiric Therapy for Gastroesophageal Reflux Disease (GERD) Patients without Alarm Features in a Primary Care Setting: A Pragmatic, Randomized, Single Blind Study****INVESTIGATORS:****Name & Signature****Unit/Position**

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**1. BRIEF DESCRIPTION**

Gastroesophageal reflux disease is a commonly encountered disorder in daily practice. Proton pump inhibitor therapy has been the cornerstone of treatment for decades. Although it has been proven to be highly effective, there is still room for improvement. A local study showed that only 57.3% of subjects are asymptomatic after 4 weeks treatment with rabeprazole. Recently a new drug was developed with better absorption, higher bioavailability, more sustained increased pH in the stomach and more targeted action to the H-K ATPase pump. Vonoprazan, belongs to a new class of acid suppressant medications, the potassium-competitive acid blocker (P-CAB). Vonoprazan has been studied and used successfully in Japan for H pylori eradication therapy, GERD, gastric and duodenal ulcers with favorable safety profile. However, to the author's knowledge, no study yet exists comparing vonoprazan to a proton pump inhibitor in the treatment of GERD outside Japan. This study aims to determine whether vonoprazan is superior to omeprazole in relieving symptoms in treatment-naïve adult patients with GERD.

**2. BACKGROUND**

Gastroesophageal Reflux Disease (GERD) is globally defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.<sup>1</sup> The Philippine Clinical Practice Guideline on the Diagnosis and Treatment of GERD defined is as a condition resulting from recurrent backflow of gastric contents into the esophagus and adjacent structures causing troublesome symptoms and/or tissue injury.<sup>2</sup> It is a commonly encountered disorder in the clinics and daily practice. A clinical diagnosis of GERD is acceptable with typical symptoms of acid regurgitation and/or heartburn is present. The Philippine guidelines state that empiric therapy can be started in GERD

patients without alarm features and don't require further laboratory exam or workup. The guideline recommends standard dose proton pump inhibitor (PPI) therapy once daily for 8 weeks as cornerstone for treatment.<sup>2</sup>

Proton pump inhibitor (PPI) therapy has been used as first line therapy of reflux symptoms for more than a decade. Even though it has been proven to be highly effective for reflux symptoms, there are still unaddressed issues. A local study by Lontok et al in 2013 evaluated response of GERD patients to rabeprazole 20mg once daily using a locally validated Frequency Scale of Symptoms of GERD (FSSG) in a primary care setting. Their study showed that a 4 week rabeprazole therapy resulting in complete resolution of individual symptoms ranging from 81.9-90.3%, with only 57.3% of all subjects being completely asymptomatic at the end of treatment.<sup>3</sup> Proton pump inhibitors also have unmet issues needing improvement. PPIs usually takes 5 days for their maximal effect<sup>4-5</sup>. Because of their slow onset of action, a significant number of patients are not sufficiently relieved after the first dose of PPI.<sup>6-7</sup> Approximately half of patients still have symptoms after 3 days of treatment<sup>7</sup>. PPIs are influenced by the cytochrome P450 (CYP) 2C19 polymorphism, with rapid metabolizers having the lowest intragastric pH compared with slow metabolizers.<sup>8-9</sup> PPIs are also not sufficiently effective in controlling nocturnal heartburn symptoms because overnight recovery of gastric acid is frequently seen, therefore causing loss of sleep and health-related reductions in quality of life.<sup>10-12</sup>

Recently, a new drug that promises better pharmacokinetic and pharmacodynamics properties was developed. Its use has been mostly in Japan for the past 2 years. Vonoprazan, is a novel, potassium-competitive acid blocker (P-CAB) that binds and inhibits H-K ATPase, the final step in acid secretion from the parietal cells of the stomach. It can inhibit the proton pump in both acidic and neutral environments with high affinity. The drug is retained for a long time inside the parietal cells and can inhibit H-K ATPase that is activated by further stimulation of acid secretion. Vonoprazan offers the advantage of not being required to be taken before meals, compared to conventional PPIs where 30 minutes before a meal is required, and is unaffected by the CYP2C19 polymorphism. Vonoprazan is also effectively absorbed and quickly accumulates in parietal cells, therefore, acid inhibition is more pronounced after the first dose of vonoprazan, compared to conventional PPIs where it usually takes 3-5 days for maximal effect. Vonoprazan is therefore, a stronger acid blocker that has rapid, stable and longer-lasting effects.<sup>13</sup> Of the author's knowledge only 2 large scale randomized controlled trial have been done with vonoprazan, both these studies were done in Japan and focus only on those with erosive esophagitis. Vonoprazan has been showed to be effective and noninferior to lansoprazole for curing erosive esophagitis, as well as PPI resistant erosive esophagitis, with healing rates more pronounced for Grade C and D erosive esophagitis.<sup>14-15</sup> Other studies on the use of vonoprazan for GERD have been done only in Japan, and comprised of noninferiority and small retrospective open label trials.<sup>16-17</sup>

When vonoprazan is used for short term acid suppression, there are no problematic side effects. Treatment emergent adverse events irrespective of causal relationship to study medication are nasopharyngitis, diarrhea, constipation, upper respiratory infection, fall, gastroenteritis and eczema. Most of these treatment emergent adverse events were classified as mild in intensity.<sup>13</sup> Studies are ongoing in Japan to assess the long term safety and efficacy of vonoprazan.<sup>13</sup>

The Philippine Clinical Practice Guideline for GERD recommends locally-validated standardized questionnaire to assess treatment response to GERD. Commonly used questionnaires in the Philippines are the Frequency Scale for Severity of GERD (FSSG) and the Gastroesophageal Reflux Disease Questionnaire (GERDQ); both have undergone local validation studies. FSSG has been shown to correlate with endoscopic severity of GERD and assess response to proton pump inhibitor therapy.<sup>2</sup> The FSSG comprises 12 questions where patients would rate individual symptoms as never (0% of the time), occasionally (around 30% of the time), sometimes (50%), often (70%) or always (100%). GERD is diagnosed if the score is more than 8, with sensitivity of 62%, specificity of 59% and accuracy of 60% for endoscopic diagnosis of esophagitis.<sup>18</sup>

Vonoprazan was just recently introduced to the Philippine market recently. Whether or not this drug may replace conventional PPIs as first line therapy remains to be determined. This study aims to determine whether vonoprazan is superior to omeprazole in treating treatment-naïve adult patients with GERD. Data from this study will help formulate policies and recommendations on the treatment of GERD, as well as formulate new treatment strategies for patients with GERD.

## **2.1 RESEARCH QUESTION**

Is vonoprazan more effective than omeprazole as empiric therapy in relieving symptoms of patients with gastroesophageal reflux disease (GERD) without alarm symptoms?

## **3. OBJECTIVES**

The objectives of this study are the following:

1. To compare the effectiveness of vonoprazan against omeprazole in relieving symptoms of GERD using the Frequency Scale of Symptoms of GERD (FSSG) questionnaire at Days 3, 7 and 14 days of treatment, specifically:
  - a. Proportion of complete responders/partial responders/nonresponders at each time point between vonoprazan group and omeprazole group
  - b. Difference in the percent change in the symptom score from baseline using the FSSG questionnaire at each time point within both groups

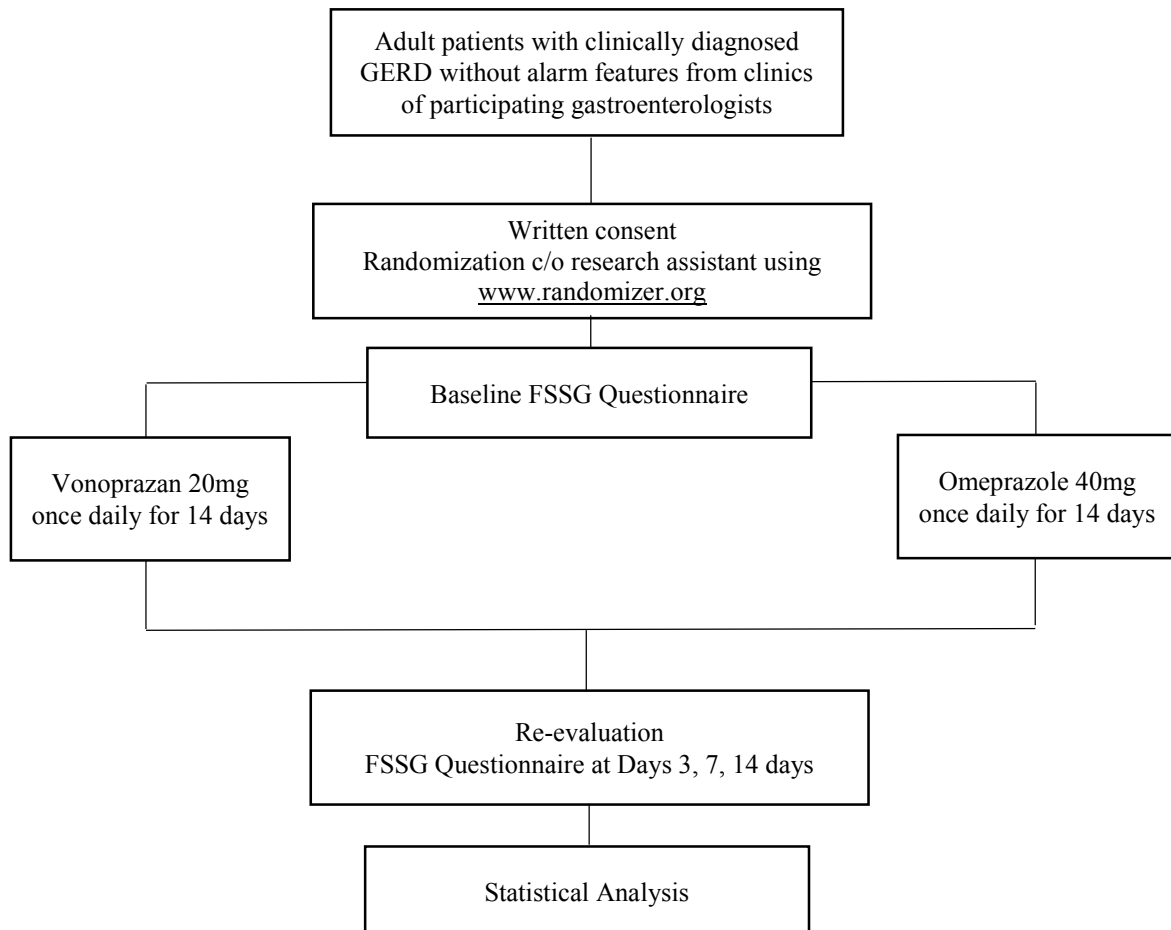
- c. Difference in the percent change in the symptom score from baseline using the FSSG questionnaire at each time point between vonoprazan group and omeprazole group
2. To assess the safety of vonoprazan compared with omeprazole in patients with clinically diagnosed GERD

#### 4. METHODOLOGY

##### 4.1 Study Design

This is a pragmatic, randomized, single blind controlled trial comparing effectiveness of vonoprazan against omeprazole in relieving symptoms of GERD. Patients clinically diagnosed with GERD will be recruited from the clinics of participating gastroenterologists. Symptoms will be assessed using the locally validated Frequency Scale of Symptoms of GERD (FSSG) questionnaire by Lontok, et.al. Adverse events will be recorded via symptom diary given to patients.

*Figure 1. Flowchart of Study Methods*



## 4.2 Participants

### Inclusion criteria

- i. All Adult patients with clinically diagnosed with Gastroesophageal Reflux Disease (GERD) without alarm features (heartburn and acid regurgitation)
- ii. Age more than 18 years at the time of written consent
- iii. Those who provide written consent with their own free will
- iv. Both treatment naïve and treatment experienced patients will be included. Treatment experienced patients should not be taking any proton pump inhibitors for 2 weeks to allow for washout period.

### Exclusion criteria

- i. Patients that have alarm features as defined by the Philippines Guidelines for GERD (dysphagia, odynophagia, weight loss, anemia, hematemesis, family history of esophageal adenocarcinoma, nocturnal choking, abdominal mass, recurrent/frequent vomiting, chest pain)
- ii. Patients with atypical GERD symptoms (cough, laryngitis, chest pain, etc.)
- iii. Patients already taking proton pump inhibitors for the past 2 weeks
- iv. Patients who scored less than 8 on the FSSG questionnaire
- v. Patients who have undergone gastroesophageal surgery
- vi. Patients who are poorly compliant to medications
- vii. Allergic to PPI or vonoprazan
- viii. With serious comorbidities, such as but not limited to: heart failure, renal failure, malignancy or hepatic failure
- ix. Pregnant, breastfeeding or possibly pregnant
- x. Patients that would not provide consent
- xi. Patients who are unable to complete the FSSG Questionnaire independently
- xii. Patients who are unable to follow up at designated periods
- xiii. Patients taking rilpivirine or atazanavir.
- xiv. Patients with elevated baseline liver function tests (more than twice the upper limit of normal)

## 4.3 Study Setting

St. Luke's Medical Center – Quezon City, a private tertiary hospital

#### 4.4 Sampling and Sample size

Sample size was calculated based on the comparison of patients with erosive esophagitis Grade C/D given a P-CAB or PPI, assuming that success rate among patients given PPI is 82.6% and among those given PCAB is 96% (Ashida, 2015), with an alpha error of 5%, power of 80% and one tailed alternative hypothesis. Sample size required is 89 per group or 178 for 2 groups; allowing for 25% dropout rate, final sample size is 224 patients.

#### 4.5 Study duration: 1 year and 6 months

#### 4.6 Outcome:

*Primary outcome:* Proportion of asymptomatic patients. Asymptomatic patients is defined as a patient being free of symptoms of heartburn or acid regurgitation according to FSSG questionnaire (score <8) on day 3, 7, and 14 of therapy.

#### *Secondary outcome:*

- a. Proportion of partial responders, nonresponders at each time point: day 3, 7, and 14 of therapy
- b. Difference in the percent change in the symptom score from baseline using the FSSG questionnaire at each time point within Vonoprazan and omeprazole group
- c. Difference in the percent change in the symptom score from baseline using the FSSG questionnaire at each time point between vonoprazan group and omeprazole group
- d. Safety and frequency of adverse effects experienced by patients (nasopharyngitis, diarrhea, constipation, upper respiratory tract infection, gastroenteritis, eczema/allergy, hypergastrinemia)

#### 4.7 Study Procedures

##### 4.7.1 Recruitment

Patients will be recruited from private and social service outpatient clinics of gastroenterologists of St. Luke's Medical Center - Quezon City. Letters of invitation will be distributed to all consultant gastroenterologists containing the inclusion and exclusion criteria of the participants. The research protocol will also be presented at the research update conference of the Institute of Digestive and Liver Diseases.

#### 4.7.2 Randomization

Patients who will give written consent will be randomized to receive either vonoprazan or omeprazole for the treatment of GERD for 14 days. Randomization will be done using an online research randomizer website: [www.randomizer.org](http://www.randomizer.org). The research assistant will handle the randomization, 224 random number assignment will be generated using the website. The research assistant will list the participants in a database containing the study drug assignment for which only the research assistant has access.

#### 4.7.3 Baseline Characteristics

Baseline characteristics will be acquired from the participants, specifically: age, sex, body mass index [BMI], smoking [never smoked, current smoker, previous smoker], alcohol consumption [daily, 2-3 days a week, 2-3 days a month, never], caffeine consumption, comorbidities [hypertension, diabetes, others] and history of GERD treatment [antacids, H2 blockers, proton pump inhibitor]. After randomization, patients on each arm will be asked to answer the locally validated FSSG questionnaire in English or Tagalog form as baseline evaluation. General data specifically the name, address, email, phone numbers, and referring physician will also be acquired.

#### 4.7.4 Participation

Once the participant is deemed eligible for the study, participants will be guided to the laboratory for blood extraction [CBC, liver function test, GGT, LDH, Creatinine]. Once the baseline laboratory parameters are acceptable, the research assistant will then give the participants a prescription containing a code to the assigned study drug, which will be dispensed by the hospital pharmacy. The research assistant may guide the study participants to the pharmacy department to procure the study medication. Patient will then continue to take their medication and asked to follow up and reevaluate their symptoms on day 3, 7 and 14 of treatment using again the FSSG questionnaire, which will be facilitated by the research assistant or the lead investigators. On day 14, after answering the FSSG questionnaire, patients will be directed to the laboratory for repeat blood examination [CBC, liver function test, GGT, LDH, Creatinine].

#### 4.7.5 Blinding

Due to difficulties in logistics, the study will follow single blinding procedures. Only the principal investigators will be blinded to the study group assignment; the research assistant and the participants will be unblinded. We recognize a potential bias to the study results may occur since study participants may compare what drugs they are taking; but since both drugs have therapeutic value, the bias as a result of nonblinding of study participants will be minimal. Coordination with the pharmacy will be done regarding coded prescription for the assigned study drug. The pharmacy will dispense labeled tablets in their original packaging from the manufacturer.

Table 1 – Study procedure/Flow	
Day 0	<ul style="list-style-type: none"><li>➤ Recruitment from Clinics</li><li>➤ Briefing and orientation on the trial c/o primary investigators (PI)</li><li>➤ Signing of informed consent form c/o primary investigators (PI)</li><li>➤ Baseline characteristics: age, sex, BMI, smoking [never smoked, current smoker, previous smoker], alcohol consumption [daily, 2-3 days a week, 2-3 days a month, never], caffeine consumption, comorbidities [hypertension, diabetes, others] and history of GERD treatment [antacids, H2 blockers, proton pump inhibitor]. General data specifically the name, address, email, phone numbers, and referring physician will also be acquired. – c/o PI or research assistant (RA)</li><li>➤ Answering of FSSG questionnaire</li><li>➤ Blood extraction (CBC, LFT, GGT, LDH, Creatinine)</li></ul>
Day 0/1	<ul style="list-style-type: none"><li>➤ Interpretation of laboratory results</li><li>➤ Screening using Inclusion and Exclusion Criteria</li><li>➤ Randomization c/o research assistant (RA)</li><li>➤ Issuance of Coded Prescription – c/o RA</li><li>➤ Proceed to Pharmacy to acquire medication</li><li>➤ Issuance of Travel allowance and notebook (symptom diary) for the next visit – P100</li></ul>
Day 1/2	<ul style="list-style-type: none"><li>➤ First intake of study medication</li></ul>
Day 4	<ul style="list-style-type: none"><li>➤ Answer FSSG Questionnaire</li><li>➤ Review of symptom diary/Interview for any adverse effects</li><li>➤ Issuance of Travel allowance</li></ul>
Day 8	<ul style="list-style-type: none"><li>➤ Answer FSSG Questionnaire</li><li>➤ Review of symptom diary/Interview for any adverse effects</li><li>➤ Issuance of Travel allowance</li></ul>
Day 15	<ul style="list-style-type: none"><li>➤ Answer FSSG Questionnaire</li><li>➤ Review of symptom diary/Interview for any adverse effects</li><li>➤ Last dose of study medication in the morning</li><li>➤ Blood extraction (CBC, LFT, GGT, LDH, Creatinine)</li></ul>
Day 43 (6 weeks)	<ul style="list-style-type: none"><li>➤ Follow up phone call for any adverse effects/events</li></ul>



#### 4.7.6 Adverse Events Reporting

Screening for adverse events will be sought at every visit for reevaluation and noted at an electronic excel file. All serious adverse events (SAE) from the start to the completion of the trial until 6 weeks after taking the medications will be collected. All SAEs will be followed up until the event is confirmed (death, recovery, or loss to follow up).

#### 4.7.7 Study Medication

This study will compare and use 2 study medications, both are branded medications and approved by the FDA. Participants will be instructed to take both tablets 30 minutes before breakfast.

<b>Table 2 – Medications to be used in the study</b>				
Drug	Dose	Brand	Manufacturer	Distributor
Omeprazole	40mg capsule	Omepron	Ajanta Pharmaceutical	United Laboratories, Inc.
Vonoprazan	20mg tablet	Vocinti	Takeda Pharmaceutical	Takeda Healthcare

<b>Table 3 – Adverse Effects of medications to be used in the study</b>	
Drug	Adverse Effects (Frequency)
Omeprazole	<ul style="list-style-type: none"><li>• Headache (7%)</li><li>• Abdominal pain (5%)</li><li>• Diarrhea (4%)</li><li>• Nausea (4%)</li><li>• Vomiting (3%)</li><li>• Flatulence (3%)</li><li>• Dizziness (2%)</li><li>• Upper respiratory tract infection (2%)</li><li>• Acid Regurgitation (2%)</li><li>• Constipation (2%)</li><li>• Rash (2%)</li><li>• Cough (1%)</li></ul>
Vonoprazan	Frequency 0.1%- less than 5% <ul style="list-style-type: none"><li>• Constipation</li><li>• Diarrhea</li><li>• Feeling of enlarged abdomen</li><li>• Nausea</li><li>• Rash</li><li>• Increased AST/ALT/ALP/LDH/GGT</li><li>• Edema</li><li>• Eosinophilia</li></ul>

#### 4.7.8 Early withdrawal and Lost to follow up

Withdrawal or premature termination from the trial may be due, but not limited to: patient's decision to withdraw, adverse events, failure to follow protocol, follow up visits, or intake of study medications, or the investigator's decision to safeguard patient's safety. The reason for premature termination/withdrawal from the trial will be noted and recorded. Participants who will withdraw prematurely will be instructed to return to their gastroenterologists for appropriate treatment of their GERD symptoms. The attending gastroenterologist will also be informed of the patient's premature termination.

In cases of participants unable to follow up strictly on designated periods, a time allowance limit of two weeks from last follow up date will be enforced; otherwise, the participant will be declared lost to follow up and will be dropped from the study. To ensure adequate follow up, all participants will be reminded to follow up with all possible means: phone call, short messaging service and electronic media (eg. Viber and Facebook Messenger).

Vonoprazan and Omeprazole are generally well tolerated and adverse effects are usually mild and well tolerated. Adverse effects are as summarized above. Patients experiencing side effects will be given appropriate management as follows: headache will be prescribed with paracetamol 500mg tablet every 6 hours as needed for headache; cough and colds will be prescribed with either acetylcysteine 600mg sachet twice a day for 5 days or a combination tablet of chlorphenamine + paracetamol + phenylpropanolamine every 6 hours for 7 days; constipation will be prescribed with polyethylene glycol 17g/sachet as needed; diarrhea will be managed expectantly, patients will be advised to increase oral fluid intake; rashes or allergies, levocetirizine 5mg/tablet for 5 days. These medications are included in the budget and will be provided to participants for free. Other medications will be prescribed as needed for unexpected minor adverse events.

Patients who have elevations of more than twice the upper limit of normal on the liver function test (ALT, AST, TPAG, Total bilirubin, direct bilirubin, indirect bilirubin, LDH, GGT) will be asked to stop taking their assigned medication and asked to repeat liver function test after two weeks to document resolution of the increase in liver function test. In cases where the liver function test still doesn't improve after two weeks, they will be referred to a hepatologist. All subsequent, professional fee, workup and medications recommended by the hepatologist will be shouldered by the study and provided to the participant for free.

#### 4.8 Data Management and Analysis:

All data collected will be plotted in an electronic excel file and secured with a password known to proponents only.

The data gathered will be described using frequency and percentage for categorical variables and mean +/- SD for continuous variables.

#### 4.9 Statistical Analysis

For the primary outcome on the proportion of complete responders, comparison of the effectiveness between PCAB and PPI will be analyzed using the chi-squared test. Risk ratio in the 95% confidence interval will also be calculated. Difference in percent change of FSSG score within groups will be computed using the paired T test. Difference in the percent change of the FSSG score between groups will be analyzed using independent T test or Mann-Whitney U test between vonoprazan and omeprazole groups at one point in time; repeat measures ANOVA will also be computed to compare percent change between different time points (baseline, day 3, 7, and 14). Comparison of adverse outcome for the 2 drugs will also be analyzed using chi-squared test. Level of significance will be set at alpha 0.05.

#### 4.10 Operational Definitions

1. Complete Responder/Asymptomatic patients - patients free of symptoms of heartburn or acid regurgitation according to FSSG questionnaire on day 3, 7, and 14 of therapy; patients who scored <8 for symptoms on the FSSG questionnaire
2. Partial Responders/GERD Symptom Relief – patients who still have GERD symptoms, but with partial improvement on reevaluation using the FSSG questionnaire; patients with at least 50% reduction from the baseline FSSG score
3. Nonresponders – Patients who reported no significant improvement in symptoms with treatment; patients with less than 50% reduction from the baseline FSSG score
4. Percent change in the symptom score –  $[\text{baseline FSSG score} - \text{re-evaluated FSSG score}]$  divided by the baseline FSSG score

#### 4.11 Ethical Considerations

The study will abide by the Principles of the Declaration of Helsinki (2013) and will be conducted along the Guidelines of the International Conference on Harmonization – Good Clinical Practice (ICH-Protocol Version 10 dated 15 December 2019)

GCP). The Clinical Protocol and all relevant documents shall be reviewed and approved by the SLMC Institutional Ethics and Review Committee. Patient confidentiality shall be respected by ensuring anonymity of patient records. Each patient document is CODED and will not contain any identifying information in order to ensure confidentiality. All study data shall be recorded and investigators are responsible for the integrity of the data i.e. accuracy, completeness, legibility, originality, timeliness and consistency. The manner of disseminating and communicating the study results shall guarantee the protection of the confidentiality of patient's data.

Study documents will be kept for 5 years after publication. Documents will be stored at the Institute of Digestive and Liver Disease – St. Luke's Medical Center, Quezon City. After five years, the documents will be shredded and burned before disposal.

No life-threatening risks are foreseen to happen to the participants of the study. The side effects of both drugs are rare, mild and transient as listed above. There is the inconvenience of having to come back on days 3, 7, and 14 for reevaluation. The study will provide P100 travel allowance per visit to participants to cover for travel expenses.

Medications for treatment of acid reflux and baseline lab exams will be provided to patients for free. Medications to treat the side effects will also be provided for free to patients as well. Results generated from this study will contribute to the advancement for the treatment of gastroesophageal reflux disease (GERD).

In cases of any adverse events or medical injury as a result of participating in this trial, participants will call/contact the primary investigators, Dr Nicodemus Ong (Phone 09176791018) and Dr Sherrie de Ocampo (Phone 09175607155) for appropriate instructions and actions. The budget for this study will include medications to treat common side effects of the drug, with provision for admission for any serious allergic reactions. The medications to treat the common side effect of the drug will be provided to participants free of charge.

## 5. COLLABORATORS/SPONSORSHIP

Researchers plan to ask for sponsorship from the research fund of St. Luke's Medical Center Quezon City, Research and Biotechnology Department. Research proponents does not plan to ask for assistance from any pharmaceutical company to minimize conflict of interest.

## 6. RESULTS

### A. Table for Collection of Raw Data

Patient Initials	Patient ID	Age	Gender	FSSG Score Baseline – Day 0	FSSG Score Day 3	FSSG Score Day 7	FSSG Score Day 14	Adverse Events Reported	Asymptomatic/ Partial responder/ Nonresponder

**Table 1. Table for Collection of Raw Data**

### B. Dummy Table for the Primary Outcome

Proportion of Complete Responders/Asymptomatic Patients			Chi-squared Test
	Vonoprazan	Omeprazole	
<b>Day 3</b>			
<b>Day 7</b>			
<b>Day 14</b>			

**Table 2. Proportion of asymptomatic patients**

### C. Dummy Table for the Secondary Outcomes

Proportion of Partial Responders/GERD Symptom Relief			Chi-squared Test
	Vonoprazan	Omeprazole	
<b>Day 3</b>			
<b>Day 7</b>			
<b>Day 14</b>			
Proportion of Nonresponders			Chi-squared Test
	Vonoprazan	Omeprazole	
<b>Day 3</b>			
<b>Day 7</b>			
<b>Day 14</b>			

**Table 3. Proportion of Partial Responders and Nonresponders**

Mean FSSG score Vonoprazan Group – each will be compared to baseline		
	Mean FSSG Score	Paired T Test
<b>Baseline</b>		
<b>Day 3</b>		
<b>Day 7</b>		
<b>Day 14</b>		
[Compare between different time points]	Repeat Measures of ANOVA	[Result of Repeat Measures of ANOVA]
Mean FSSG score Omeprazole Group – each will be compared to baseline		
	Mean FSSG Score	Paired T Test
<b>Baseline</b>		
<b>Day 3</b>		
<b>Day 7</b>		
<b>Day 14</b>		
[Compare between different time points]	Repeat Measures of ANOVA	[Result of Repeat Measures of ANOVA]

Table 4. **Mean FSSG Score within Vonoprazan and Omeprazole Groups**

<b>Adverse Events</b>	<b>Vonoprazan (number of patients)</b>	<b>Omeprazole (number of patients)</b>	<b>F test</b>
Nasopharyngitis			
Diarrhea			
Constipation			
Upper respiratory infection			
Gastroenteritis			

Eczema/Allergy/Eosinophilia			
Increased SGPT			
Increased SGOT			
Increased ALP			
Increased Bilirubin			
Increased GGT			
Increased LDH			

**Table 5. Adverse events**

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**APPENDIX A**  
Frequency Scale for the Symptoms of GERD (FSSG) questionnaire

Date			
Patient ID		Age	
		Gender	

Question		Never (0%)	Occasion ally (30%)	Somet imes (50%)	Often (70%)	Always (100%)
<b>1</b>	Do you get heartburn?	0	1	2	3	4
<b>2</b>	Does your stomach ever get bloated?	0	1	2	3	4
<b>3</b>	Does your stomach ever feel heavy after meals?	0	1	2	3	4
<b>4</b>	Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
<b>5</b>	Do you ever feel sick after meals?	0	1	2	3	4
<b>6</b>	Do you get heartburn after meals?	0	1	2	3	4
<b>7</b>	Do you have an unusual (eg burning) sensation in your throat?	0	1	2	3	4
<b>8</b>	Do you feel full while eating meals?	0	1	2	3	4
<b>9</b>	Do some things get stuck when you swallow?	0	1	2	3	4
<b>10</b>	Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
<b>11</b>	Do you burp a lot?	0	1	2	3	4
<b>12</b>	Do you get heartburn if you bend over?	0	1	2	3	4
Total						
Total Score						

**APPENDIX B**  
**Frequency Scale for the Symptoms of GERD (FSSG) questionnaire**  
**Locally Validated**

Petsa			
Patient ID		Edad	
		Kasariaan	

Tanong		Hindi (0%)	Sobrang Minsan (30%)	Minsan (50%)	Madalas (70%)	Lagi (100%)
1	Kinakabagan ka ba?	0	1	2	3	4
2	Nakakaramdam ka ba ng sakit, hapdi o init sa sikmura na gumuguhit paakyat hanggang dibdib? (Nakakaramdam ka ba ng “heartburn?”)	0	1	2	3	4
3	Humahapdi/sumasakit baa ng iyong sikmura kahit hindi pa nakakain?	0	1	2	3	4
4	Nakakaranas ka ba ng “Heartburn” kapag nakakain ka ng mga piling pagkain? (Nakakaranas k aba ng sakit, hapdi, o init sa sikmura na gumuguhit paakyat hanggang dibdib kapag nakakain ng mga piling pakain?)	0	1	2	3	4
5	Sumasama ba ng iyong pakiramdam kapag naparami ang nakain?	0	1	2	3	4
6	Nakakaramdam ka ba ng pamumuno ng sikmura kaagad pagkatapos kumain?	0	1	2	3	4
7	Sumasama baa ng iyong pakiramdam kapag hinihigpitan ang iyong tiyan?	0	1	2	3	4
8	May nalasahan ka bang maasim na umaakyat hanggang bibig?	0	1	2	3	4
9	Mayroon bang maiinit na pakiramdam sa sikmura na umaakyat hanggang dibdib?	0	1	2	3	4
10	Mabigat ba ang iyong sikmura pagkatapos kumain?	0	1	2	3	4
11	Sumasama baa ng iyong pakiramdam pagkatapos kumain ng mamantika/matatabang pagkain?	0	1	2	3	4
12	Madalas ka bang dumighay?	0	1	2	3	4
Total						
Total Score						

## **APPENDIX C**

Product Insert of Omeprazole 40mg capsule [Omepron] and Vonoprazan 20mg tablet [Vocinti]

## B. Proposed Budget

See attached Budget Proposal

## C. GANTT CHART

ACTIVITY	Sept to Nov 2018	Dec 2018 to March 2020	Feb to March 2020	March to April 2020
Research/Writing of Protocol				
Presentation to IRB				
Data Gathering				
Data Interpretation				
Writing of Final Paper				
Presentation of Final Paper				
Editing				