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Research Article

Efficacy and Safety of Tegoprazan in Patients with Erosive Gastroesophageal Reflux Disease- A Multi-country, Prospective, Randomized, Double-Blind, Active-Controlled, Parallel-Group Study.

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Short running title: Efficacy and Safety of Tegoprazan in Erosive Gastroesophageal Reflux Disease

Abstract

Background: Tegoprazan is a highly selective potassium-competitive acid blocker (P-CAB) that delivers rapid relief and maintains an intragastric pH above 4 after both single and multiple doses.
Objective: This study was aimed to determine the efficacy and safety of Tegoprazan in treating erosive gastroesophageal reflux disease (eGERD) over a treatment period of 8 weeks.
Methods: The present study was a randomized, double-blind, active-controlled, parallel-group multi-center, multi-country phase 3 clinical trial to evaluate efficacy and safety of Tegoprazan 50 mg tablet in comparison to Esomeprazole 40 mg tablet in patients with eGERD. The study planned to enroll male and non-pregnant female patients (18-65 years of age) with endoscopically confirmed eGERD classified as Los Angles (LA) grades A-D. Following a screening period of approximately 14 days, eligible patients were randomized in 1:1 ratio to one of the two double-blind treatment groups. The primary endpoint was the cumulative endoscopic healing rate of eGERD by 8 weeks based on the upper gastrointestinal (GI) endoscopy. Symptoms, safety, and tolerability were also assessed. This trial is registered at Clinical Trial Registry of India (CTRI) and South African National Clinical Trial Registry (SANCTR).
Results: Between November 2023 and July 2024, in a competitive recruitment process spanning three countries, 255 patients were enrolled: 179 from India, 69 from Russia, and 7 from South Africa. At week 8, cumulative endoscopic healing rate for Tegoprazan was 99.1% [95% CI: 95.25:99.98] and with Esomeprazole was 97.2 % [95% CI:92.17:99.43], demonstrating the non-inferiority of Tegoprazan to Esomeprazole, with a p-value <0.0001. Treatment emergent adverse events (TEAEs) were comparable in both groups and Tegoprazan was well tolerated. TEAEs that occurred in ≥1% of patients were headache, diarrhea, nausea, and abdominal pain.
Conclusions: Tegoprazan was non-inferior to Esomeprazole and safe for patients with eGERD.

Keywords: Tegoprazan, Potassium competitive acid blocker, Gastroesophageal Reflux, Esophagitis, Endoscopy.

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KEY SUMMARY

Summarize the established knowledge on this subject

- The evidence supports the use of potassium-competitive acid blockers (P-CABs), which offer a potent and reversible inhibition of gastric H+/K+-ATPase. Tegoprazan, a highly selective P-CAB, delivers rapid relief and maintains an intragastric pH above 4 after both single and multiple doses.
- In a phase III study from South Korea, once daily administration of Tegoprazan 50 or 100 mg exhibited non-inferior efficacy in healing erosive esophagitis and tolerability to that of esomeprazole 40 mg after 8 weeks of treatment.

What are the significant and/or new findings of this study?

- In the present phase III clinical trial, the cumulative endoscopic healing rate for Tegoprazan demonstrated non-inferiority to Esomeprazole in patients with erosive gastroesophageal reflux disease (eGERD).
- This is the first study of Tegoprazan in patients with eGERD from India, Russia, and South Africa. Tegoprazan could add to the therapeutic armamentarium in this difficult to treat condition.

INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a prevalent digestive disorder characterized by typical heartburn or several symptoms caused by the reflux of gastric acid or food into the esophagus. On a global scale, the prevalence of GERD is approximately 13.98%, with significant regional variations ranging from 12.88% to 22.40%.[1] In India, the rates are alarmingly high, ranging from 7.6% to 30%,[2] and a concerning 10% of these patients suffer from erosive gastroesophageal reflux disease (eGERD). In Russia, GERD prevalence ranges from 13.3 to 23.6% in different regions.[3] According to a study conducted in Nigeria, a typical African population, the overall prevalence of GERD was estimated to be 7.6 % and it appears that this observation is close to the prevalence in Asia (2.5 % to 7.8 %). [4,5]

GERD is classified into two categories: non-erosive reflux disease (NERD) and eGERD. The treatment aims not only to relieve symptoms but also to heal erosive esophagitis (EE) and prevent recurrences and complications that significantly diminish patients' quality of life. And, if untreated, may lead to Barrett's esophagus and can cause diseases such as esophageal ulcers, strictures or malignancy.[6]

Proton pump inhibitors (PPIs) have long been the cornerstone of GERD treatment, recommended for both initial management and relapse. Their effectiveness is closely tied to maintaining an intragastric pH above 4, which is vital for the healing of severe eGERD classified as Los Angeles (LA) grades C and D. Nonetheless, PPIs come with notable limitations. Their slow onset of action and inability to entirely suppress acid production (up to 30 % suboptimal efficacy)[7-9] can lead to nighttime acid breakthrough, leaving patients vulnerable to discomfort. Despite the availability of different treatment options for GERD, the quest for an unmet need for drugs in the treatment of patients with GERD continues.

A promising alternative is the potassium-competitive acid blocker (P-CAB), which offers a potent and reversible inhibition of gastric H+/K+-ATPase.[10-13] P-CABs provide a faster onset of action and prolonged suppression of gastric acid secretion, positioning them as a superior choice for managing eGERD. Tegoprazan, a highly selective P-CAB, delivers rapid relief within 1 hour and maintains an intragastric pH above 4 after both single and multiple doses.[14,15]

Tegoprazan was approved as a treatment for GERD, gastric ulcer and *H. pylori* infection in South Korea and for eGERD, duodenal ulcer and *H. pylori* infection in China. The clinical development program for Tegoprazan included a phase 2 dose-ranging study, which demonstrated that endoscopic healing (efficacy end point) by week 8 were comparable between Tegoprazan (50 to 200 mg, once daily) and Esomeprazole (40 mg, once daily).[16] For the current study, the dose of 50 mg Tegoprazan and 40 mg Esomeprazole was selected based on findings of safety and efficacy in phase 3 trial from South Korea. In a randomized, double-blind phase 3 study by Lee et al. 2018,[17] Tegoprazan 50 mg or 100 mg was shown to be non-inferior efficacy to Esomeprazole 40 mg in eGERD patients after 8 weeks of treatment. Use of Tegoprazan also provided better symptomatic relief, along with improvement in GERD-Health Related Quality of Life scores (GERD-HRQL).

The objective of the present trial was to evaluate the efficacy and safety of a once-daily dose of Tegoprazan 50 mg compared to Esomeprazole 40 mg by 8 weeks of treatment in patients with endoscopically confirmed eGERD grades A-D.

MATERIALS AND METHODS

Study design and participants

This was a prospective, multi-country, multicenter, randomized, active controlled, double blind, parallel group, phase 3, 8-week study comparing once daily dose of Tegoprazan 50 mg or Esomeprazole 40 mg. Patients were enrolled from India, Russia and South Africa. The study design was aimed to establish the non-inferiority of Tegoprazan 50 mg to Esomeprazole 40 mg.

The study planned to recruit eligible male and non-pregnant female patients aged 18 to 65 years (inclusive) who had endoscopically confirmed eGERD classified as LA grades

A-D along with symptoms of heart burn and regurgitation. Major exclusion criteria included the presence of esophageal stricture, ulcer stricture, gastroesophageal varices, Barrett's esophagus, active gastric or duodenal ulcers, gastrointestinal bleeding or malignancies confirmed on an upper GI endoscopy, eosinophilic esophagitis, a history of acid-lowering surgery, previous esophageal or gastric surgery, any malignancy prior to enrollment, primary esophageal motility disorders, irritable bowel syndrome, inflammatory bowel disease, or any of the following abnormal laboratory test values at screening: blood urea nitrogen and serum creatinine levels exceeding 1.5 times the upper limit of normal (ULN); total bilirubin levels and serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyltransferase exceeding 2 times the ULN. Pregnant and lactating women, as well as patients requiring treatment with nonsteroidal anti-inflammatory drugs (except for low dose aspirin (≤100 mg/day) taking prior to study participation for prophylactic use) including cyclooxygenase-2 (COX-2) inhibitors were also excluded from the study. Any female of childbearing potential who was sexually active was required to use adequate contraceptive measures during the study period. Furthermore, patients were not allowed to use any concomitant medications that could influence the efficacy evaluation, including proton pump inhibitors, histamine receptor 2 blocking agents, prostaglandins, mucosal protective agents, antidepressants, antipsychotics, and antianxiety drugs. Additionally, patients who tested positive for *H. pylori* at screening were ineligible to enter the study. Use of rescue medication (antacids such as Gelusil/ Gaviscon or other hydroxide/bicarbonate based medication as available in the participating countries) was permitted, and this was to be recorded in the subject diary, for consideration during the efficacy analysis.

The study consisted sequentially of a screening period of 14 days, followed by the randomized double-blind treatment period lasting upto 8 weeks. During the screening period, endoscopy was performed to assess the presence and severity of eGERD, using the LA classification system. Follow-up endoscopies were performed at week 4 or week 8. Healed eGERD was defined as the absence of esophageal mucosal erosions or ulcers on endoscopy.

Any reliable, documented results available from an endoscopy performed in a routine clinical setting (demonstration of LA Grade A-D of eGERD) and *H.Pylori* test (rapid urease test/13C/14C Urea breath test as per the applicable country practice) within 14 days prior to randomization (before signing of informed consent) were accepted in the study (given the invasive nature of the endoscopy procedure). Patients were instructed to maintain usual food intake, sleep habits, consistent activity, and caffeine intake throughout the study, and were asked to refrain from consumption of alcohol and tobacco use, excessive drinking and eating, and any extreme diet change or excessive exercise. Patients were deemed compliant if they administered between 80% and 120% of the prescribed doses during the treatment period. Compliance was assessed by examining the medications returned and patient diary entry.

Intervention and randomization

Randomization of patients was done in a ratio of 1:1 using interactive web response system (IWRS) for the test (Tegoprazan 50 mg) and comparator (Esomeprazole 40 mg) arm. Per assignment, each randomized patient had to self-administer one tablet each of Tegoprazan (test) and matching placebo of Esomeprazole or one tablet each of Esomeprazole (comparator) and matching placebo of Tegoprazan once a day, orally, every day for upto 8 weeks. All the eligible patients received the study treatment (test or comparator) for a duration of 4 weeks. An additional one month of treatment was provided to the participants who did not achieve endoscopic healing at week 4. Study medication was dispensed on the day of randomization, and week 4 (if the endoscopic healing was not achieved), using IWRS.

Allocation concealment

The allocation of a unique number for investigational products to each patient was managed by a third party who was not associated with the study site personnel. Allocated unique numbers were not disclosed until the statistical analysis, except for emergencies like the incidence of serious adverse events (SAE). Group assignment was concealed from patients, investigators, clinical research organization (CRO), sponsors, and data analysts.

Implementation of blinding

A double-dummy method, using matching Tegoprazan and Esomeprazole placebo tablets, was employed to ensure that the study was double-blinded. Blinding was achieved by formation of individual therapeutic kits for patients including active drug tablets and placebo tablets. The patients and investigators (and other personnel involved in the study) were unaware of the study drug(s) administered to the patients. The CRO and sponsor were also blinded during the study.

Study objectives and outcomes

The study was designed to confirm the non-inferiority of Tegoprazan 50 mg to Esomeprazole 40 mg in patients with eGERD. The primary efficacy endpoint was the cumulative endoscopic healing rate of eGERD by 8 weeks based on the upper GI endoscopy. Each patient's cumulative endoscopic healing rate was calculated using the following formula: cumulative endoscopic healing rate = (the number of patients who had the endoscopic healing / the number of patients

who were treated at LA grade) x 100. Patients who achieved endoscopic healing within 4 weeks of study treatment were included in analysis of the primary endpoint.

The secondary efficacy endpoint included the healing rate of eGERD at 4 week based on the upper GI endoscopy following 4 weeks of study treatment. Healing rate at week 4 from the initiation of study treatment was defined as follows: Healing rate at week 4 (%) = (the number of patients who had the endoscopic healing until week 4/the number of patients who were treated until Week 4 and had an upper GI endoscopy) x 100.

Other secondary efficacy endpoints were based on subjective symptom assessments as recorded by patients on their daily symptom diaries. Additionally, the patient-reported outcome measures included GERD-Health-Related Quality of Life (GERD-HRQL) scores.

Safety was evaluated through physical examination and the analysis of treatment emergent adverse events (TEAEs), laboratory results and vital signs. Each AE was classified by severity-mild, moderate, or severe by the investigator. Treatment-emergent adverse event was defined as an adverse events (AEs) newly occurred after the randomization and the first administration of study medication.

Determination of sample size

Assuming a power of 85 %, level of significance 2.5 %, non-inferiority margin of 10 %,18 a total of 254 patients were required to be enrolled in the study and randomized in a ratio of 1:1 to test and comparator arms.

Statistical analysis

All descriptive and inferential statistical analyses were performed using SAS® version 9.4 in a secure and validated environment, unless otherwise noted. Statistical significance was concluded when the p-value was less than 0.05. The frequency and percentage of cumulative endoscopic healing rate of eGERD for visit (up to week 4 or week 8) by treatment group based on the upper GI endoscopy was presented as 95 % confidence interval (CI) for the proportion difference evaluated using Miettinen-Nurminen (MN) method. P-value was calculated using Wald Method for the Miettinen-Nurminen test. 95% CI for proportion for each treatment were calculated using Clopper-Pearson method. The non-inferiority of Tegoprazan 50 mg to Esomeprazole 40 mg was concluded when the lower limit of its two-sided 95% CI was larger than the non-inferiority margin of 10%. For continuous variables, the number of patients, mean, median, standard deviation, 1st and 3rd quartiles, minimum and maximum were evaluated. The difference in the mean change was tested using the paired t-test or Wilcoxon signed rank test based on normality of data.

Efficacy assessments were performed in the per-protocol set (PPS) and complementarily in the full analysis set (FAS). All randomized patients (intention-to-treat) who met inclusion/exclusion criteria, administered at least one dose of assigned investigational product and had at least one post-dose evaluation of the primary estimate were included in the FAS population. The PPS population was defined as all patients in the FAS who did not withdraw from the study without participation for the whole treatment period, completed the primary endpoint evaluation at week 8 (or 4), received the study treatment to which they were randomized, and exhibited treatment compliance of at least 80% with no significant protocol deviation.

All safety analyses were based upon the safety set (SS) population. Safety set was defined as patients who received at least one dose of investigational product and had at least one post-dose safety assessment.

Data collection and management

During the study, patients filled out daily diaries to record the details (presence) of major symptoms (heartburn and regurgitation), use of concomitant medications, rescue medication and adverse events over an 8-week treatment period. Patients were instructed to complete the diary every morning upon waking and every evening before going to sleep.

Presence of major symptoms were evaluated using patient diary. Additional measures included GERD-health related quality life (GERD-HRQL) scores and treatment compliance. The GERD-HRQL scale featured 11 items focusing on symptoms, dysphagia, medication effects, and overall health, with scores ranging from 0 to 5, where higher scores indicated worse quality of life.

Case record forms (CRFs) were used to collect information required for data analysis. When the database was declared to be complete and accurate, the database was locked and unblinded.

Ethical considerations

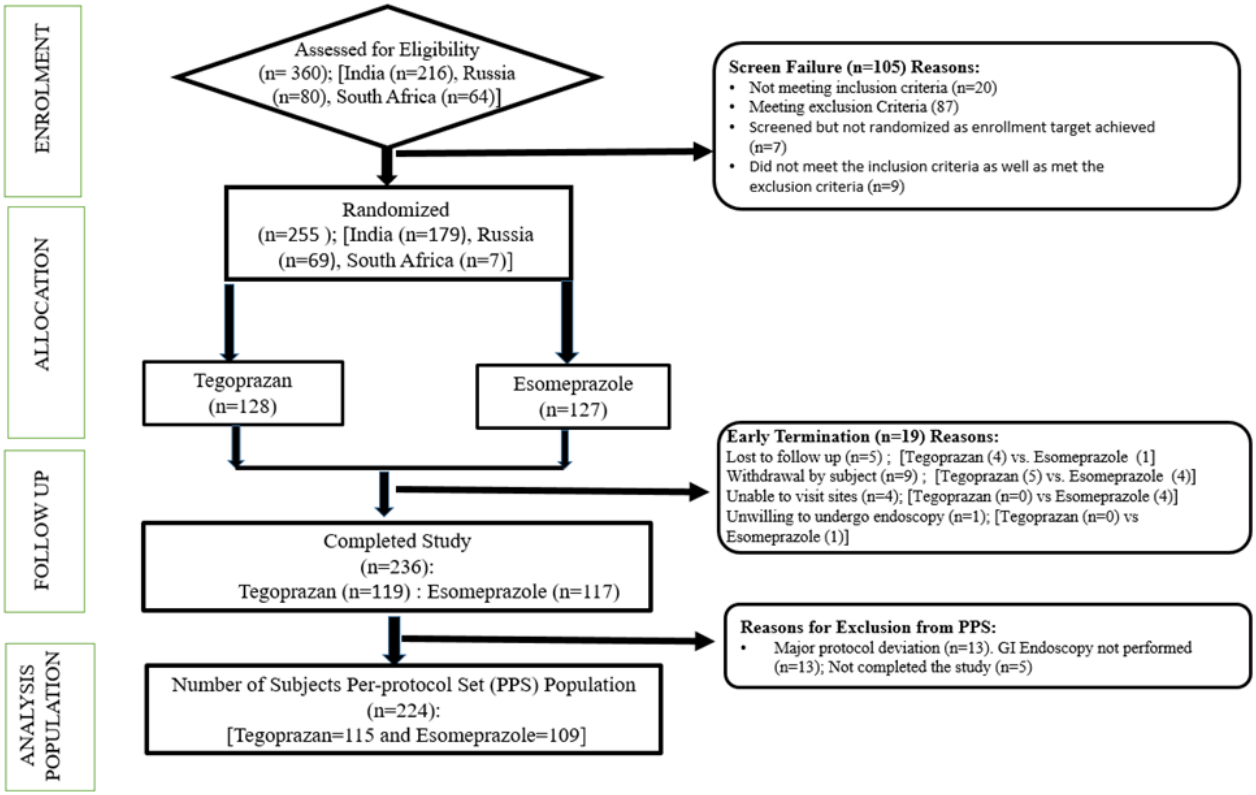
The study was conducted in compliance with the ethical principles that originate in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP). The study was approved by the applicable regulatory authorities and institutional ethics committees of each participating centres of the respective countries. Written informed consent was obtained from each patient prior to screening on the approved informed consent form (ICF). This trial has been registered at CTRI with the Trial Registration number CTRI/2023/11/059403 and at SANCTR with Trial Registration DOH-27- 062023-8876 (The final protocol for the study is provided as a supplementary file-appendix 1).

RESULTS

Study population characteristics

Between November, 2023, and July, 2024, a total of 360 patients were screened at 19 centers across India (13 sites), Russia (4 sites) and South Africa (2 sites), of which 255 patients were randomized and 105 patients were screen failures (**Figure 1**). These 255 patients were enrolled with competitive recruitment across the three countries. Out of 255 randomized patients, 254 (99.6%) were included in the SS, 224 (87.8%) in PPS and 241 (94.5%) were part of FAS.

Figure 1. CONSORT diagram displaying the flow of participants through the study



In the SS population, 137 (53.9%) were male and 117 (46.1%) were female. The median age of enrolled patients was 38.0 years (ranging from 18 to 64 years). The mean (SD) baseline body mass index (BMI) was 25.5 (4.74) kg/m2. Among the safety set population, the majority of the patients were Asian (182, 71.7%), followed by Russian (67, 27.5%), and Black African (2, 0.8%) (**Table 1**). The frequencies for LA grade A/B/C/D was 75.78%/18.75%/3.13%/2.34% and 76.19%/18.25%/3.97%/1.59% in the Tegoprazan and Esomeprazole groups, respectively. Demographic characteristics were comparable between the two treatment groups. In the SS population, the mean (SD) for treatment compliance at week 4 was 99.5 % (4.62) [99.9 % for Tegoprazan and 99.1 % for Esomeprazole]. At week 8, the overall mean (SD) of treatment compliance for the 23 eligible patients was 99.8 % (2.19) [100.0 % for Tegoprazan and 99.7 % for Esomeprazole].

Table 1. Summary of baseline demography

Demographic Variable	Statistic	Tegoprazan 50 mg (N=128)	Esomeprazole 40 mg (N=126)	Overall (N=254)	P-Value
Age (Year)	Mean (SD)	40.5 (11.56)	39.9 (10.99)	40.2 (11.27)	0.6443
	Median (min-max)	38.5 (18.0:64.0)	38.0 (19.0:63.0)	38.0 (18.0:64.0)	
Gender	Female	60 (46.9%)	57 (45.2%)	117 (46.1%)	0.7936 (C)
	Male	68 (53.1%)	69 (54.8%)	137 (53.9%)	0.7936 (C)
BMI (Kg/m^2)	Mean (SD)	25.2 (4.12)	25.7 (5.30)	25.5 (4.74)	0.8244(w)
	Median (min-max)	24.9 (16.2:47.8)	24.3 (16.7:50.2)	24.7 (16.2:50.2)	

Race	Asian	93 (72.7%)	89 (70.6%)	182 (71.7%)	0.7208 (C)
	African	1(0.8%)	1(0.8%)	2(0.8%)	>0.9999(F)
	Russian	34 (26.6%)	36(28.6%)	70(27.5%)	0.8279 (C)
Baseline LA Classification	LA grade A	97(75.78%)	96(76.19%)	193(75.98%)	0.9392(C)
	LA grade B	24(18.75%)	23(18.25%)	47(18.50%)	0.9189(C)
	LA grade C	4(3.13%)	5(3.97%)	9(3.54%)	0.7480(F)
	LA grade D	3(2.34%)	2(1.59%)	5(1.97%)	>0.9999(F)

Abbreviations: *SD, Standard deviation; BMI, Body mass index; cm, centimeter; kg, kilogram; m, meter; min-max, min-imum-maximum; LA, Los Angeles Demographic characteristics were compared between treatment groups using Chi-square (C) or Fisher's exact test(F) for p-value calculation. P value <0.05 was considered significant.*

Abbreviations: *SD, Standard deviation; BMI, Body mass index; cm, centimeter; kg, kilogram; m, meter; min-max, min-imum-maximum*

Efficacy results

In the PP population [N=224 (Tegoprazan=115 and Esomeprazole=109), at week 8, the cumulative endoscopic healing rate observed in the Tegoprazan group was 99.1% [95% CI;95.25:99.98], which was comparable to the observed in the Esomeprazole group at 97.2% [95% CI; 92.17:99.43]. The percentage difference amounted to 1.88% (95% CI: -1.63:5.39), demonstrating non-inferiority of Tegoprazan to Esomeprazole, with a p-value <0.0001. At week 4, The percentage difference in healing rate between the Tegoprazan and Esomeprazole groups was 1.35% [95% CI; 5.96: 8.66], exhibiting non-inferiority of Tegoprazan with p-value of <0.0001. (**Table 2**). In the FAS population, the healing rates at week 4 and week 8 were also comparable. For both PP and FAS analysis population, the lower bound of the two-sided 95% CI of the treatment difference met the prespecified non-inferiority criteria at 4 and 8 weeks of treatment.

Table 2. Summary of Categorical Efficacy Variable

Per-Protocol (PP) population (N=224)						
Categorical efficacy variable	**Tegoprazan 50 mg (N=115)**		**Esomeprazole 40 mg (N=109)**		**Percentage Difference [95%CI]**	**P Value**
	Frequency	**Percentage (%) [95% CI]**	**Frequency**	**Percentage (%) [95% CI]**		
Endoscopic healing rate of eGERD by 8 week	114	99.1% [95.25:99.98]	106	97.2 [92.17:99.43]	1.88 [-1.63:5.39][1]	<0.0001[2]
Endoscopic Healing rate of eGERD at 4 week	106	90.2 [85.66 : 96.36]	99	90.8 [83.77 : 95.51]	1.35 [-5.96 : 8.66][1]	0.0012 [2]
Full Analysis Set (FAS) population (N=241)						
Categorical efficacy variable	**Tegoprazan 50 mg (N=122)**		**Esomeprazole 40 mg (N=119)**		**Percentage Difference [95%CI]**	**P Value**
	Frequency	**Percentage (%) [95% CI]**	**Frequency**	**Percentage (%) [95% CI]**		
Endoscopic healing rate of eGERD by 8 week	118	96.7 [91.82:99.10]	112	94.1 [88.26:97.60]	2.6 [-2.67:7.88][1]	<0.0001[2]
Endoscopic Healing rate of eGERD at 4 week	110	90.2 [83.45:94.81]	104	87.4 [80.06:92.77]	2.77 [-5.20:10.74][1]	0.0008[2]

[1] 95% CI for proportion difference between treatment arms was calculated by using Miettinen-Nurminen method.

[2] p-value was obtained using Wald Method for the Miettinen-Nurminen test.

Abbreviations: *eGERD, Erosive gastroesophageal reflux disease; CI, Confidence interval*

The percentage of days without major symptoms was seen to improve in both groups and was comparable during the 8-week treatment period. Likewise, the decrease in average GERD-HRQL scores for the Tegoprazan-treated group was similar to that of the Esomeprazole group (**Table 3**).

Additionally, the percentage of days without rescue medication was more than 98% for both Tegoprazan and Esomeprazole at week 8, showing an increase with each assessment visits. (**Table 3**).

Table 3. Summary of Continuous Efficacy Variable.

Continuous Variable	Tegoprazan 50 mg (N=122)	Esomeprazole 40 mg (N=119)	Overall	P Value
	Mean (SD)	Mean (SD)	Mean (SD)	
Percentage of days without major symptoms (heartburn and regurgitation)				
Upto week 1	N=78 58.4 (30.67)	N=75 53.9 (31.00)	N=153 56.2 (30.81)	
Upto week 2	N= 106 56.9 (30.53)	N=93 54.1 (30.75)	N=199 55.6 (30.59)	0.5498 (w)[1]
Upto week 4	N= 119 65.4 (25.95)	N=113 62.1 (27.24)	N=232 63.8 (26.58)	0.3275 (w)[1]
Upto week 8	N=121 66.0 (26.11)	N=118 63.7 (26.52)	N=239 64.8 (26.28)	0.4867 (w)[1]
Percentage of days without major symptoms during the daytime				
Upto week 1	N= 94 63.7 (31.59)	N=90 59.7 (30.26)	N=184 61.8 (30.93)	
Upto week 2	N=109 68.5 (27.44)	N=97 66.8 (25.68)	N=206 67.7 (26.57)	0.5362 (w)[1]
Upto week 4	N=119 75.1 (22.59)	N=113 73.3 (22.16)	N=232 74.2 (22.35)	0.4469 (w)[1]
Upto week 8	N=120 75.0 (22.65)	N=114 74.0 (21.88)	N=234 74.5 (22.24)	0.5980 (w)[1]
Percentage of days without major symptoms during the night-time				
Upto week 1	N=91 61.7 (31.79)	N=85 63.8 (30.78)	N=176 62.7 (31.24)	
Upto week 2	N=109 66.9 (28.12)	N=102 63.0 (30.35)	N=211 65.0 (29.22)	0.4083 (w)[1]
Upto week 4	N=119 75.5 (21.97)	N=113 73.9 (22.81)	N=232 74.7 (22.35)	0.6565 (w)[1]
Upto week 8	N=121 75.8 (22.24)	N=119 74.4 (23.33)	N=140 75.1 (22.75)	0.7008 (w)[1]
Percentage of days without rescue medication				
Upto week 1	N=108 95.2 (9.74)	N=103 95.5 (10.16)	N=211 95.3 (9.92)	
Upto week 2	N=114 97.2 (5.72)	N=104 97.1 (6.18)	N=118 97.2 (5.93)	0.8470 (w)[1]
Upto week 4	N=120 98.4 (3.78)	N=114 98.3 (3.62)	N=234 98.3 (3.70)	0.8567 (w)[1]
Upto week 8	N=122 98.0 (5.41)	N=119 98.3 (3.51)	N=241 98.2 (4.57)	0.9829 (w)[1]

Continuous Variable	Tegoprazan 50 mg (N=122)			Esomeprazole 40 mg (N=119)			Overall		P Value
	Actual Mean (SD)	Difference Mean (SD)	P-value	Actual Mean (SD)	Difference Mean (SD)	P-value	Actual Mean (SD)	Difference Mean (SD)	
Mean change in GERD-HRQL (GERD-Health related quality life) score									
Upto week 2	N=122 8.0 (5.62)	-7.7 (7.13)	<0.0001 (w)[2]	N=118 9.1 (6.19)	-8.7 (7.77)	<0.0001 (w)[2]	N=240 8.5 (5.92)	-8.2 (7.45)	0.5294 (w)[3]
Upto week 4	N=122 3.2 (3.97)	-12.4 (7.54)	<0.0001 (w)[2]	N=119 3.9 (4.31)	-13.8 (8.17)	<0.0001 (w)[2]	N=241 3.6 (4.15)	-13.1 (7.87)	0.1315 (w)[3]
Upto week 8	N=9 2.6 (1.42)	-9.4 (6.80)	0.0031 (t)[2]	N=13 3.8 (5.91)	-13.5 (7.09)	<0.0001 (t)[2]	N=22 3.3 (4.60)	-11.8 (7.10)	0.2159 (w)[3]

1] p-values were obtained using two sample t-test(t)/Wilcoxon rank-sum test(w) and used to compare between treatments based on normality test.
2] p-values were obtained using Paired t-test(t)/Wilcoxon signed rank test(w) and used to compare within treatment based on normality test.
3] p-values were obtained using two sample t-test(t)/Wilcoxon rank-sum test(w) and used to compare between treatments based on normality test.

Abbreviations: *GERD-HRQL, GERD-Health related quality of life; SD, Standard deviation*

Safety results

Of the 254 patients in SS population, TEAEs by system organ class (SOC) and preferred term (PT) observed in at least 1% of patients were headache 5.1% (Tegoprazan 6.3% vs Esomeprazole 4%), diarrhoea 2.8% (Tegoprazan 2.3% vs Esomeprazole 3.2%), nausea 2.4% (Tegoprazan 3.1% vs Esomeprazole 1.6%) and upper abdominal pain 2.4% (Tegoprazan 2.3% vs Esomeprazole 2.4%). The TEAEs occurred in at least 1% of patients were comparable in the Tegoprazan and Esomeprazole groups (**Table 4**). The majority (92.7%) of TEAEs were considered mild in severity. No potential life-threatening TEAEs or death was reported in the study in any arm throughout the study. No clinically significant abnormalities were observed in vital signs, clinical laboratory parameters, and physical examination data.

Table 4. TEAEs by system organ class (SOC) and preferred term (PT) in ≥1% of patients –safety set population

	Tegoprazan 50 mg (N=128)	**Esomeprazole 40 mg (N=126)**	**Overall (N=254)**
TEAEs (≥1% of patients) by SOC and PT	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal Disorders			
Diarrhoea	3(2.3%)	4(3.2%)	7(2.8%)
Nausea	4(3.1%)	2(1.6%)	6(2.4%)
Abdominal Pain Upper	3(2.3%)	3(2.4%)	6(2.4%)
Abdominal Distension	2(1.6%)	3(2.4%)	5(2.0%)
Abdominal Pain	2(1.6%)	3(2.4%)	5(2.0%)
Dry Mouth	2(1.6%)	2(1.6%)	4(1.6%)
Eructation	3(2.3%)	1(0.8%)	4(1.6%)
Flatulence	2(1.6%)	1(0.8%)	3(1.2%)
Constipation	2(1.6%)	1(0.8%)	3(1.2%)
Nervous System Disorders			
Headache	8(6.3%)	5(4.0%)	13(5.1%)
Dysgeusia	2(1.6%)	1(0.8%)	3(1.2%)
Investigations			
Alanine Aminotransferase Increased	0(0.0%)	3(2.4%)	3(1.2%)
Blood Alkaline Phosphatase Increased	0(0.0%)	3(2.4%)[3]	3(1.2%)
Red Blood Cell Sedimentation Rate Increased	0(0.0%)	3(2.4%)	3(1.2%)
Infections And Infestations			
Influenza	0(0.0%)	3(2.4%)	3(1.2%)
Urinary Tract Infection	1(0.8%)	2(1.6%)	3(1.2%)

Treatment Emergent Adverse Events represented as: Patient count (Percentage of patients)
Adverse Events coded using MedDRA version 27.0.
A patient might have reported more than one adverse event.
Abbreviations: *TEAEs, Treatment emergent adverse events,*

DISCUSSION

The current randomized controlled study conducted in India, Russia and South Africa, involving 255 patients clearly established that Tegoprazan, administered at 50 mg once daily, was non-inferior to Esomeprazole at 40 mg with respect to the healing rates of eGERD after continuous once daily treatment over a period of 8 weeks (or 4 weeks). PP analyses of the healing rate following the 4-week and 8-week treatment were complemented by the non-inferiority of Tegoprazan 50 mg to Esomeprazole 40 mg observed in FAS population. These findings are also consistent with the previous phase 2 dose ranging study, and 8-week randomized phase 3 trials from South Korea elucidating the effects of Tegoprazan on eGERD healing.[16,17]

A decrease in the mean GERD-HRQL score, was observed with both the investigational product. On the other subjective secondary endpoints viz., percentage of days without major symptoms and no major symptoms during daytime and nighttime, Tegoprazan exhibited comparable improvements at all assessment visits upto 8 weeks, similar to Esomeprazole group. Furthermore, the percentage of days without needing rescue medication was also similar in the treatment groups. These findings corroborate the observed outcome in previous studies. [16,17]

To our knowledge, this is the first double-blind, active-controlled study unequivocally demonstrating the non-inferior efficacy and safety of Tegoprazan as compared to Esomeprazole in patients with eGERD from India, Russia, and South Africa. Patients with eGERD severity across the LA grades spectrum (A-D) were recruited from centers within these countries, making the observed outcomes quite generalizable to the eGERD population. While the authors acknowledge possible limitations including but not limited to potential difficulties in scoring system comprehension and study diary compliance in individual patients, a lesser representation of patients from South Africa, the reliance on patient memory to evaluate voluptuary behaviors—which is prone to recall bias, the exclusion of patients who tested positive for *H. Pylori*, as well as those diagnosed with IBS or IBD; the findings are justifiably robust. The TEAE profile of Tegoprazan was similar to that of Esomeprazole. In particular, consistent with other phase 3 studies, the most common TEAEs observed were gastrointestinal events. Overall, Tegoprazan was found to be generally safe and well-tolerated over 4 and 8 weeks of treatment. There were no SAEs or deaths reported in the study.

In conclusion, the present study confirms that Tegoprazan, a novel potassium-competitive acid blocker, is as effective as Esomeprazole for treating erosive gastroesophageal reflux disease in patients from India, Russia, and South Africa, with good tolerability. Tegoprazan can be a valuable addition to the treatment options for difficult to treat erosive gastroesophageal reflux disease.

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Conflict Of Interest/Disclosure Statement

PA, BKJ, JM, SD, SKC, and SRW are full time employees of Dr. Reddy's Laboratories Ltd. GSS is full time employee of HK Inno.N Corp. The authors RB, RP, and BRS are the trial investigators and they declared that no competing interests exist. The authors RB, RP, and BRS entered into a contract for the patient recruitment and clinical conduct of the study at their respective sites.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Author Contributions

PA conceived and designed the study. SRW managed the collection of the study data. SKC analysed the data. PA, SD, SKC, BKJ, JS interpreted the data. BKJ prepared drafts of the article. PA, SD, JS, SRW, GSS critically reviewed the article. RB, RP, and BRS recruited patients and reviewed the article. PA approved the article to be communicated for publication.

Ethical Consideration

The study was approved by institutional ethics committee of each centre in the participating countries. Written informed consent was obtained from each patient prior to screening on the approved informed consent form (ICF). The study was conducted in compliance with the ethical principles that originate in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP) and applicable regulatory requirements.

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