BMJ Open Gastroenterology

Analysis of the symptom response to esomeprazole 20 mg over days 1–4 of a 14-day course of treatment for frequent heartburn: results of two randomised controlled trials

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To cite: Peura D, Le Moigne A, Wassel H, *et al*. Analysis of the symptom response to esomeprazole 20 mg over days 1–4 of a 14-day course of treatment for frequent heartburn: results of two randomised controlled trials. *BMJ Open Gastro* 2019;**6**:e000278. doi:10.1136/bmjgast-2019-000278

Data from this paper were previously presented at Digestive Disease Week 2016, 21–24 May 2016, San Diego, California.

Received 18 January 2019
Revised 10 May 2019
Accepted 24 May 2019

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ABSTRACT

Background Drug exposure and corresponding antisecretory effects increase over the first 4–5 days of esomeprazole treatment. To date, this effect has not been correlated with symptomatic improvement. Therefore, the efficacy of esomeprazole was evaluated on days 1–4 and 5–14 using pooled data from two identical randomised, double-blind, placebo-controlled studies conducted in subjects with frequent heartburn who are likely to self-treat with over-the-counter medications.

Methods Adults without confirmed diagnoses of gastro-oesophageal reflux disease experiencing heartburn 2 or more days per week in the past 4 weeks were randomly assigned to treatment with esomeprazole 20 mg or placebo once daily for 14 days following a 1-week placebo run-in period (esomeprazole: n=330; placebo: n=321). Heartburn episodes were documented in daily diaries. The current analyses evaluated the change in baseline percentage of heartburn-free days across days 1–4 and 5–14.

Results Change in the percentage of heartburn-free days from the run-in was significantly greater with esomeprazole compared with placebo ($p<0.001$) starting on days 1–4. The greatest treatment benefit was observed during days 5–14. During this period, esomeprazole-treated subjects increased their heartburn-free time over the run-in period by 32.5% compared with 14.3% with placebo ($p<0.001$).

Conclusions Frequent heartburn sufferers treated with esomeprazole 20 mg had significantly more heartburn-free days relative to placebo throughout the studies. Maximal clinical benefits coincided with the estimated timing of maximal pharmacokinetic and pharmacodynamic effects and duration of acid control on days 5–14.

Trial registration number NCT01370525; NCT01370538

Summary box

What is already known about this subject?

- Exposure to the active compound in proton-pump inhibitors (PPI) is thought to correspond with their antisecretory effects. However, this effect has not yet been shown to correlate with symptomatic improvement.

What are the new findings?

- These analyses showed that the peak symptomatic benefits observed with esomeprazole 20 mg coincided with the estimated timing of maximal pharmacokinetic and pharmacodynamic effects. Although the greatest clinical benefit was observed 5–14 days after initiating treatment, analyses of data from day 1 to day 4 also revealed significant benefits for esomeprazole 20 mg over placebo. These benefits were observed regardless of subjects' pretreatment heartburn frequency.

How might it impact on clinical practice in the foreseeable future?

- Individuals who self-treat their frequent heartburn with over-the-counter (OTC) esomeprazole can expect symptomatic improvement independent of the frequency of heartburn they are experiencing. The benefits begin during the first 4 days of treatment but peak during days 5–14. The observed symptomatic response should help to set appropriate expectations for individuals who self-treat their frequent heartburn with OTC PPI and may be used to inform secondary treatment options if optimal treatment response is not observed during the expected time period.

INTRODUCTION

Symptoms associated with gastro-oesophageal reflux, including heartburn and acid regurgitation, are common in the general population and can negatively impact daily functioning and quality of life.[1–4] Due to the extensive availability of effective non-prescription treatment options for the management of frequent heartburn, individuals may choose to self-treat these symptoms rather than seek help from a healthcare provider.[5 6] The increasing availability of over-the-counter (OTC) proton-pump inhibitors (PPI)

provides an opportunity to improve the quality of care for individuals experiencing frequent heartburn who do not wish to consult a healthcare provider to receive treatment for their symptoms.[6]

The efficacy of the PPI esomeprazole 20 mg in the OTC setting has been demonstrated in two randomised, double-blind, placebo-controlled phase III clinical trials conducted in adults with frequent heartburn.[7] The recommended course of treatment for OTC PPI is to take them once every day for 14 days. Because of their established pharmacokinetic and pharmacodynamic profiles, PPI are not intended to provide immediate heartburn relief. Treatment for 1–4 days may, therefore, be required to produce their full therapeutic benefit.[8 9] The onset of effect of PPI is thought to be related to their pharmacokinetics and pharmacodynamics,[10] which suggest that drug exposure and the degree of acid inhibition increase progressively over the first several days of treatment.[11] Pharmacokinetic assessments have shown that the esomeprazole area under the plasma concentration curve (AUC) and peak plasma concentrations (C_{max}) increase nearly twofold between day 1 and day 5 with the administration of 20 mg once daily.[11 12] Decreased systemic elimination and increased bioavailability due to reduced first pass metabolism are the primary factors driving the observed increase in PPI exposure over the first few days of treatment.[11 12] Pharmacodynamic studies have expanded on these data by showing a clear correlation between the AUC and C_{max} of esomeprazole and omeprazole and the degree of acid inhibition.[11 13] In addition, inhibiting all gastric acid pumps with a single dose of an oral PPI is not possible since not all pumps are active during the relatively short half-life of PPI.[14] The objective of these analyses was to explore the efficacy of esomeprazole 20 mg during the initial 4 days of treatment and over the subsequent days of treatment (days 5–14 of the 14-day regimen), which coincides with the time that maximal acid inhibition is thought to be reached.

METHODS

NEXT-1 and NEXT-2 (study 1 and study 2) were two identical randomised, double-blind, placebo-controlled phase III studies designed to determine the efficacy of a 14-day regimen of esomeprazole 20 mg for the treatment of frequent heartburn in subjects who are likely to self-treat with OTC medications without consulting a healthcare provider. Both studies were approved by the relevant institutional review boards and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the studies.[7] The conduct of these studies, which were registered on ClinicalTrials.gov under identifiers NCT01370525 and NCT01370538, has been described in detail previously[7] and is summarised here briefly. Data from these two studies were pooled for the current analyses.

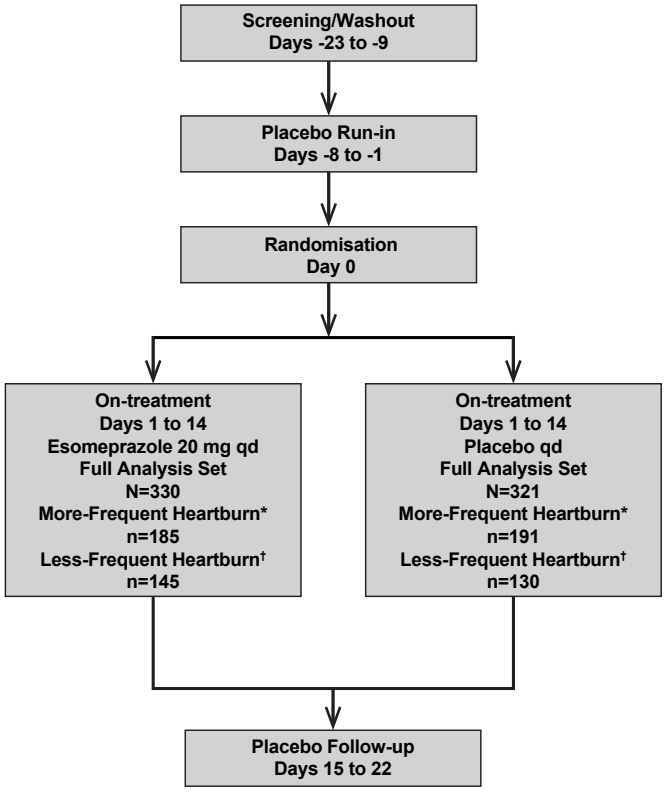

Figure 1 Study design. *More frequent heartburn defined as 6 or more days of heartburn during the run-in period. †Less frequent heartburn defined as fewer than 6 days of heartburn during the run-in period. qd, once a day.

Study design

Both studies enrolled male and female subjects aged ≥18 years who had been experiencing frequent heartburn on 2 or more days per week over the prior 4 weeks. Exclusion criteria included a confirmed diagnosis of gastro-oesophageal reflux disease (GORD) or any history of erosive oesophagitis, current use of a prescription medication for GORD or a need for long-term prescription therapy with histamine H_2 receptor antagonists (H_2RA), PPI, gastric prokinetic drugs or antacids for any indication.[7]

Figure 1 provides an overview of the study design. Following washout of current heartburn medication (1 or more days for antacids and 7 or more days for H_2RAs and/or PPI), eligible subjects were enrolled in a 1-week placebo run-in period. At the end of this period, subjects who continued to meet inclusion criteria and were compliant with reporting heartburn symptoms were randomly assigned to receive 14 days of double-blind treatment with either esomeprazole 20 mg capsules (administered as esomeprazole magnesium trihydrate 22.3 mg) or a matching placebo. At the end of the treatment phase, all subjects entered a 1-week, single-blind, placebo follow-up period. Subjects were instructed to take one dose of study drug per day prior to eating their morning meal. Antacid tablets (Gelusil tablets; WellSpring Pharmaceutical, Sarasota, Florida, USA) were permitted as rescue medication for breakthrough symptoms; however,

use of other prescription or OTC heartburn treatments was prohibited during the study period.[7]

Efficacy endpoints for current analyses

The primary efficacy endpoint of interest was the change from baseline in percentage of heartburn-free 24-hour days during the 14 days of treatment as measured in daily self-assessment diaries. The results for the percentage of heartburn-free 24-hour days over the 14-day treatment period have been published previously.[7] Additionally, analyses were conducted on the mean change from baseline for 24 hours' heartburn intensity, which was rated as: 0=none; 1=mild; 2=moderate; and 3=severe. Using pooled data from the two studies, the current analyses evaluated these outcomes across days 1–4 (a planned secondary endpoint in the two trials) and days 5–14 to assess the efficacy of esomeprazole before and after peak pharmacological effects are expected to occur.

Subgroup analyses were also conducted in subjects who were classified as experiencing more frequent and less frequent heartburn during the run-in period. More frequent heartburn was defined as 6 or more days of heartburn during the run-in period, and less frequent heartburn was defined as fewer than 6 days of heartburn during the same period.

Statistical analyses

The analyses presented in this report are based on pooled data for the full analysis set from NEXT-1 and NEXT-2. The full analysis set consisted of all randomised subjects who received at least one dose of randomised study treatment and recorded at least one baseline and postbaseline efficacy measurement. The number of heartburn-free days for the study periods of interest and the entire 2-week study period was collected using daily subject diary data. A percentage of heartburn-free time was calculated by summing the number of recorded heartburn-free days and dividing by the length of the period (ie, 4, 7, 10 or 14 days). Between-group differences in change from baseline in the percentage of heartburn-free 24-hour days and heartburn intensity were evaluated using a mixed linear model analysis with study centre within study and treatment as fixed effects. For the primary endpoint, the percentage of heartburn-free days during the run-in period was included as a covariate. All statistical tests were two sided, with a significance level of 5% (α=0.05), unless otherwise specified.

RESULTS

Subject disposition and baseline demographics

A total of 651 subjects were included in the full analysis set. The baseline demographic characteristics for the total population are presented in table 1.

The baseline demographics for the more and less frequent heartburn subgroups were balanced between treatment groups. Among these subjects, 376 (58%) experienced heartburn for 6 or more days during the run-in period and 275 (42%) experienced heartburn for fewer than 6 days during the run-in period. Overall, the mean number of days with heartburn during the run-in period was 5.7–5.8 for the full analysis set. The mean number of days with heartburn during the run-in period was 7.0 days for the more frequent heartburn group and 3.9–4.0 days for the less frequent heartburn group. Subjects with more frequent heartburn had higher mean (SD) 24-hour heartburn intensity scores (esomeprazole 20 mg: 1.4 (0.42); placebo: 1.4 (0.46)) than those with less frequent heartburn (esomeprazole 20 mg: 0.8 (0.30); placebo: 0.7 (0.30)) during the run-in period. There were no significant differences between subjects with more frequent and less frequent heartburn with respect to baseline demographics, although those with more frequent heartburn tended to be slightly older than those with less frequent heartburn (44.7 years vs 41.9 years, respectively).

Table 1 Baseline demographics

Characteristic	Full analysis set	
	Esomeprazole 20 mg (n=330)	Placebo (n=321)
Age (years)		
Mean (SD)	42.7 (13.1)	44.4 (13.0)
Female, n (%)	190 (57.6)	177 (55.1)
Race, n (%)		
White	208 (63.0)	219 (68.2)
Black/African-American	112 (33.9)	99 (30.8)
Asian	0 (0)	1 (0.3)
Native Hawaiian/Pacific Islander	1 (0.3)	0 (0)
American Indian/Alaskan native	4 (1.2)	0 (0)
Other	5 (1.5)	2 (0.6)
Run-in days with heartburn, mean (SD)		
Full analysis set	5.7 (1.8)	5.8 (1.8)
More frequent*†	7.0 (1.0)	7.0 (1.0)
Less frequent‡§	4.0 (1.0)	3.9 (1.0)
Run-in heartburn intensity score, mean (SD)		
Full analysis set	1.1 (0.48)	1.1 (0.52)
More frequent*†	1.4 (0.42)	1.4 (0.46)
Less frequent‡§	0.8 (0.30)	0.7 (0.30)

*More frequent heartburn defined as 6 or more days of heartburn during the run-in period.
†Esomeprazole: n=185; placebo: n=191.
‡Less frequent heartburn defined as fewer than 6 days of heartburn during the run-in period.
§Esomeprazole: n=145; placebo: n=130.

Change in percentage of heartburn-free days and heartburn intensity

During the run-in period, subjects experienced on average 5.7–5.8 days of heartburn, which represents a proportion of only 20% of heartburn-free days (table 2).

Table 2 Percentage of 24-hour heartburn-free days (full analysis population; pooled data set)

Study period	Group	Percentage of heartburn-free days, mean (SE)	Heartburn-free days, n*		Adjusted mean (SE) change from baseline in percentage of heartburn-free days	P value for difference between groups†
			In time period	Per week		
Run-in‡	ESO 20 mg	20.1 (1.2)	1.4	1.4	–	–
	Placebo	20.0 (1.3)	1.4	1.4	–	
Days 1–4	ESO 20 mg	43.1 (2.1)	1.7	3.0	24.9 (1.8)	<0.001
	Placebo	29.0 (1.9)	1.2	2.0	10.8 (1.8)	
Days 5–14	ESO 20 mg	50.8 (2.1)	5.1	3.6	32.5 (1.6)	<0.001
	Placebo	32.4 (1.8)	3.2	2.3	14.3 (1.6)	

*The number of heartburn-free days per period and week was calculated by multiplying the percentage of heartburn-free time by the number of days in the period (4, 7 or 10 days, respectively).
†Statistical comparison based on percentage of heartburn-free days.
‡A 7-day run-in period was planned for both studies; however, the actual run-in period varied between subjects. For the run-in period, the percentage of heartburn-free days was calculated using all available data. The number of heartburn-free days was calculated by multiplying the percentage of heartburn-free days by 7.
ESO, esomeprazole.

Overall, the change in the percentage of heartburn-free days from the run-in period to the end of the 14-day treatment period was significantly greater with esomeprazole 20 mg than placebo (p<0.001; figure 2A). Furthermore, the change in the percentage of heartburn-free days from the run-in period was significantly greater with esomeprazole 20 mg compared with placebo (p<0.001) starting with the day 1–4 time period and continuing through days 5–14 (table 2). In the full analysis set, mean heartburn intensity scores decreased to a significantly greater degree in the subjects treated with esomeprazole 20 mg versus placebo beginning on days 1–4 (difference: −0.2 (95% CI −0.2 to −0.1); p<0.001) and extending to days 5–14 (difference: −0.2 (95% CI −0.3 to −0.1); p<0.001; table 3).

The greatest therapeutic benefit was observed from day 5 to day 14 of the treatment period (table 2, figure 2A). During this time, subjects treated with esomeprazole 20 mg increased their heartburn-free time over the run-in period by 32.5% compared with 14.3% with placebo (p<0.001). When the percentage of heartburn-free time for this time period is standardised to a 7-day period, there is an estimated heartburn-free frequency rate of 3.6 days/week vs 2.3 days/week for the esomeprazole 20 mg group versus the placebo group, respectively, compared with an estimated 1.4 days/week for the run-in period. When the percentage of heartburn-free time for the initial 4 days of treatment was standardised to a 7-day period, the estimated frequency of heartburn-free days was 3.0 days/week and 2.0 days/week for esomeprazole 20 mg and placebo, respectively. A similar pattern of results was observed in the subgroup analysis of subjects with more and less frequent heartburn during the run-in period. Significant increases in the percentage of heartburn-free days for all time intervals were observed in both groups.

As shown in figure 2B,C, subjects with more frequent heartburn experienced a greater degree of therapeutic benefit with esomeprazole 20 mg than those with less frequent heartburn. There was little change in the mean percentage of heartburn-free days among subjects receiving placebo during the different time intervals, regardless of the frequency of heartburn experienced during the run-in period. However, there was a greater improvement in mean change from baseline on days 1–4 and days 5–14 in the percentage of heartburn-free days among those with more frequent heartburn during the run-in period relative to those with less frequent heartburn. The mean number of heartburn-free days/week among more frequent heartburn sufferers treated with esomeprazole 20 mg increased an estimated 2.5 days from the run-in period to the day 5–14 interval, when the change in least squares mean percentage of heartburn-free days is converted to the number of heartburn-free days and standardised to a 7-day period. Among less frequent sufferers treated with esomeprazole 20 mg the number of heartburn-free days/week increased an estimated 2.0 days from the run-in to days 5–14 when the change in least squares mean percentage of heartburn-free days is standardised to a 7-day period. In both the less and more frequent heartburn groups, smaller changes from baseline intensity scores were observed during days 1–4 in relation to days 5–14.

DISCUSSION

The primary data from the individual studies that were analysed here reported a significantly greater likelihood of experiencing heartburn-free days on days 1–4 with esomeprazole 20 mg compared with placebo (study 1: OR 1.81; 95% CI 1.19 to 2.74; p=0.0053; study 2: OR 2.54; 95% CI 1.66 to 3.88; p<0.0001).[7] By day 14, the proportion of esomeprazole-treated subjects who were symptom

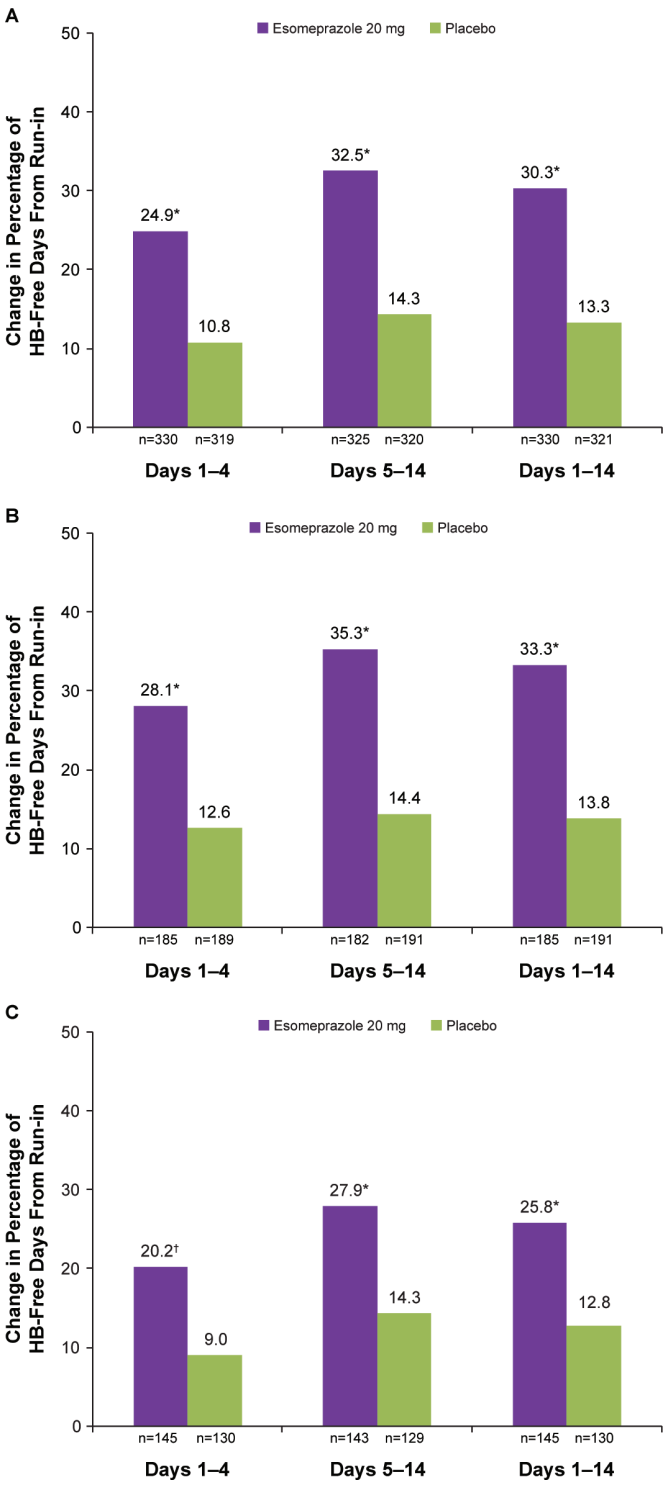

Figure 2 Change in the least squares mean percentage of heartburn-free days from the run-in period. (A) In the full analysis set. (B) In subjects with more frequent heartburn (defined as 6 or more days of heartburn during the run-in period). (C) In subjects with less frequent heartburn (defined as fewer than 6 days of heartburn during the run-in period). *p<0.001 versus placebo. †p=0.004 versus placebo. HB, heartburn.

free had increased to 46% and 48% in study 1 and study 2, respectively, for esomeprazole 20 mg, which was significantly higher than placebo (33% for both studies; p<0.0001). In clinical trials conducted with omeprazole 20 mg and lansoprazole 15 mg, the percentage of heartburn-free days was significantly higher beginning on day 1 versus placebo (p≤0.001), with this benefit extending as treatment continued to day 14.[15 16] In agreement with these studies, the current analyses demonstrate that subjects experiencing frequent heartburn who were treated with esomeprazole 20 mg once daily had significantly more days free of heartburn and had lower mean heartburn intensity scores relative to placebo during the first 4 days of treatment. However, the maximal clinical effects seen with esomeprazole 20 mg occurred in the day 5–14 period, with the change from baseline percentage of heartburn-free days increasing from 24.9% on days 1–4 to 32.5% on days 5–14. Similar but less pronounced effects were observed in the change in mean heartburn intensity scores in subjects with more frequent pretreatment heartburn episodes. This increase in heartburn control coincides with the timing of maximal pharmacokinetic and pharmacodynamic effects seen with esomeprazole 20 mg in prior studies.[11 12] In pharmacokinetic studies, esomeprazole C_{max} and AUC nearly doubled between day 1 and day 5. Andersson *et al* further demonstrated that the observed increases in esomeprazole and omeprazole exposure over the first 5 days of treatment correlated with increased inhibition of pentagastrin-stimulated gastric acid secretion.[11] A post hoc analysis conducted with data from the same studies as the current analyses explored the effects of the degree and timing of treatment response to esomeprazole 20 mg on continued symptomatic response following the end of the 2-week treatment course.[17] The results suggest that a higher level of pretreatment heartburn severity is associated with a lesser likelihood of sustained symptomatic resolution during the week after treatment cessation. Conversely, experiencing symptomatic resolution during the treatment period, particularly during the last week of treatment, increases the likelihood of experiencing sustained resolution after the end of 2 weeks of treatment with esomeprazole 20 mg. The relationship, if any, between these effects and the pharmacokinetics and pharmacodynamics of esomeprazole is unclear at this point but should be an area for future research.

We believe that the current analyses are the first to attempt to demonstrate that the maximal clinical effect of esomeprazole 20 mg in the OTC setting occurs during the estimated period of maximal effect on 24 hours' gastric pH. However, a key weakness of these analyses is that, due to their post hoc nature, esomeprazole plasma concentrations collected over the course of the study were not available. As a result, it was not possible to directly correlate the incidence of heartburn-free days with esomeprazole exposure over the course of the study. However, as detailed above, results of prior in-depth pharmacokinetic and pharmacodynamic studies have clearly delineated the time course of maximum esomeprazole exposure and acid inhibition.[11 12] Future studies seeking to investigate the relationship between the clinical

Table 3 Differences in change from baseline in 24 hours' heartburn intensity scores

	Heartburn intensity, LSM (SE)		
	Days 1–4	Days 5–14	Days 1–14
	Full analysis set		
Esomeprazole 20 mg	n=330 0.76 (0.04)	n=325 0.63 (0.03)	n=330 0.68 (0.03)
Placebo	n=319 0.95 (0.03)	n=320 0.89 (0.03)	n=321 0.91 (0.03)
Difference (95% CI) between groups in change from baseline; p value	−0.2 (−0.2 to −0.1);<0.001	−0.2 (−0.3 to −0.1);<0.001	−0.2 (−0.3 to −0.1);<0.001
	More frequent heartburn*		
Esomeprazole 20 mg	n=185 0.95 (0.05)	n=182 0.82 (0.05)	n=185 0.86 (0.04)
Placebo	n=189 1.18 (0.04)	n=191 1.13 (0.04)	n=191 1.15 (0.03)
Difference (95% CI) between groups in change from baseline; p value	−0.2 (−0.3 to −0.1);<0.001	−0.2 (−0.3 to −0.1);<0.001	−0.2 (−0.3 to −0.1);<0.001
	Less frequent heartburn†		
Esomeprazole 20 mg	n=145 0.52 (0.04)	n=143 0.40 (0.03)	n=145 0.45 (0.04)
Placebo	n=130 0.62 (0.04)	n=129 0.54 (0.04)	n=130 0.56 (0.03)
Difference (95% CI) between groups in change from baseline; p value	−0.1 (−0.3 to 0.0); 0.027	−0.2 (−0.3 to −0.1);<0.001	−0.2 (−0.3 to −0.1); 0.002

*More frequent heartburn defined as 6 or more days of heartburn during the run-in period.
†Less frequent heartburn defined as fewer than 6 days of heartburn during the run-in period.
LSM, least squares mean.

efficacy of PPI and their pharmacokinetic profiles should seek to determine plasma concentrations at various intervals over the course of study.

Although the current analyses were retrospective in nature and not specifically designed to investigate the time of maximal clinical effect of esomeprazole 20 mg, all of the data used were prospectively collected. Importantly, the primary endpoint of these studies was the percentage of heartburn-free 24-hour days during the 14-day treatment period. Furthermore, key secondary endpoints included the resolution of heartburn during the first and second weeks of treatment and the proportion of subjects with 0, 1, 2, 3 and 4 heartburn-free days during days 1–4.[7] The results reported here, therefore, are closely based on the prospective primary and secondary endpoints of the two studies.

These analyses demonstrated that individuals with both less frequent heartburn (fewer than 6 days of heartburn) and more frequent heartburn (6 or more days of heartburn) during the run-in period had significant improvements in the percentage of heartburn-free days during all stages of the on-treatment period. This suggests that individuals who are likely to self-treat their frequent heartburn with OTC esomeprazole can expect improvement in symptoms independent of the frequency of heartburn they are experiencing. Those with more severe heartburn derived greater clinical benefit from esomeprazole. Individuals with more frequent heartburn experienced a 35.3% increase from baseline in the proportion of heartburn-free days during days 5–14, compared with a 27.9% increase for those with less frequent heartburn. It is likely that this difference is due to the greater potential for improvement in the group with more frequent heartburn. Notably, however, some of the subjects in the more frequent heartburn category may not have been appropriate candidates for receiving OTC PPI and may have had a more severe condition than frequent heartburn. A similar result has been observed with obese patients.[18] In that study, it was suggested that patients with higher body mass indexes (BMI) may derive greater therapeutic benefit from PPI than leaner patients due to a correlation between higher BMI and greater baseline symptom severity and frequency. However, it is also possible that some of those with less frequent heartburn in the current analyses were misdiagnosed since subjects did not undergo endoscopy at screening or 24-hour pH monitoring. Bytzer *et al* suggested that the lower response in patients with non-erosive reflux disease compared with

those with reflux oesophagitis may have been due to the presence of functional heartburn not associated with reflux, which is not expected to respond to PPI.[19]

Although we believe these analyses provide interesting results, some additional analyses should be considered for future research efforts in this area. Specifically, an analysis of daily treatment response during the first 4 days individually may have provided additional insights by potentially showing how many individuals did or did not respond to treatment on each of those days. Additionally, performing analyses using individual subject data, as opposed to population-based means, would allow for analyses that evaluate subjects who do not respond to treatment.

CONCLUSIONS

These analyses demonstrated that frequent heartburn sufferers treated with esomeprazole 20 mg once daily had significantly more days free of heartburn relative to placebo during the first 4 days of treatment and throughout the course of the 14-day study. However, consistent with the label for OTC esomeprazole, maximal clinical effect coincided with the estimated time of maximal esomeprazole exposure and pharmacodynamic effect, which occurs on day 5. The clinical effects of esomeprazole 20 mg were sustained until the end of the 14-day treatment period. Additionally, subjects with both more frequent and less frequent heartburn at baseline benefited from treatment with esomeprazole 20 mg.

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Funding The studies were funded by AstraZeneca, which entered into an agreement with Pfizer for the over-the-counter (OTC) rights for NEXIUM (esomeprazole magnesium). These post hoc analyses were conducted by Pfizer Consumer Healthcare with data from studies conducted by AstraZeneca. AstraZeneca was involved with the design and data collection of the original studies, and Pfizer Consumer Healthcare was involved with the design of the analyses reported herein, as well as the decision to submit this manuscript for publication. Medical writing support was provided by Dennis Stancavish, MA, of Peloton Advantage, an OPEN Health company, and was funded by Pfizer. This manuscript includes data owned by AstraZeneca.

Competing interests DP reports personal fees from Takeda and Horizon outside the submitted work and has served as a consultant for AstraZeneca, Pfizer, Takeda and Horizon. ALM, HW and CP are former employees of Pfizer Consumer Healthcare.

Patient consent for publication Not required.

Ethics approval The original studies were approved by the relevant institutional review boards and conducted in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available in a public, open access repository.

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