STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Not applicable.
ACTIVE INGREDIENT: Not applicable.

Study No: D9120N00005

Developmental Phase: NIS
Study Completion Date: 12 January2010
Date of Report: 9 November 2010

OBJECTIVES

Primary objectives

The primary objectives of this observational study of patients with GERD who are partial-responders to PPI treatment were:

- To describe common treatment pathways, including extent of and time to referral to specialists;
- To collect and describe resource utilization data;
- To collect relevant cost estimates and to calculate the cost per patient;
    - To estimate the cost of illness of partial responders to PPI in the USA (using data from published literature to support this extrapolation)
- To assess the symptom load, impact of symptoms on daily life and effect on work productivity;
    - To describe the symptoms of GERD;
    - To describe the quality of life (based on generic and disease-specific instruments);
    - To describe the productivity loss

Secondary objective

The secondary objective of this study was to estimate the proportion of partial-responders to PPI therapy to all patients with GERD.

METHODS:

This was a multi-center, cross-sectional study with a 6 month retrospective data capture and prospective follow-up for 6 months, conducted in the USA. 552 adult (18 years or older) patients with GERD who were identified as partial-responders to PPI treatment were enrolled at 52 sites in the USA (out of the 81 activated sites) to obtain an evaluable target sample size of 400 patients (actual: 404 patients) at the 6-month follow-up survey.
The study involved a retrospective method of data collection using physician chart abstraction (to collect data for the 6 months preceding enrolment) and prospective data collection using patient surveys at enrolment visit, 3 months and 6 months post-enrolment. The chart abstraction data was collected on a case report form (CRF) completed by the study physician. The patient survey at baseline was completed in the physician office at the enrolment visit and the two follow-up patient surveys at 3 and 6 months were mailed to the patient. A summary of each assessment conducted appears in Table 1.

A log of all patients with GERD seen in the physician's office was maintained throughout the enrolment period of the study to provide denominator information for estimation of the prevalence of partial responders to PPI amongst patients with GERD (the study's secondary objective).

Table 1. Study Assessments and Administration Schedule

	Administration Schedule		
Study Assessments	**Enrolment Visit**	**3 months**	**6 months**
Physician CRF			
Eligibility and demographics	X		
Medical chart record abstraction (6 months retrospectively)	X (+ 2 weeks)		
Patient Survey			
Resource Utilization Related to GERD – hospital visits – physician's office visits – prescriptions – over the counter medication		X	X
Hospital Anxiety and Depression Scale (HADS)	X		
Reflux Disease Questionnaire (RESQ-7)*	X	X	X
GERD Questionnaire (GERDQ)	X		X
Quality of Life in Reflux and Dyspepsia – Reflux Inhibition (QOLRAD-RI)**	X	X	X
EuroQol 5-Dimension Questionnaire (EQ-5D)	X		X
Short Form 36 Version 2 (SF-36v2)	X		X
Work Productivity and Activity Impairment – for Patients with Gastroesophageal Reflux Disease (WPAI-GERD)	X	X	X

* RESQ-7 is a questionnaire based on the RDQ, in which subjects are asked to rate the frequency and intensity of 13 GERD symptom items over the past 7 days, using 6-point Likert scales ranging from Did not have to Daily/Severe.

** QOLRAD-RI is a version of the QOLRAD, with 25 items in which subjects are asked to report the frequency/magnitude of the effects of reflux symptoms (e.g. heartburn or regurgitation) on different aspects of their daily life during the previous week, using a 7-point Likert scale ranging from one (all of the time/a great deal) to seven (none of the time/none at all).

Inclusion Criteria

1. Provision of signed informed consent.
2. Able to read and write in US English, and able to comply with study requirements.
3. Female or male, aged 18 years or above.
4. Either by the time of the enrolment visit or some time in the past, the patient had to reach the status of partial responder to PPI treatment as defined by the following criteria:
    a. At least 6 months documented history of GERD symptoms (need not to be consecutive).
    b. Treated with unchanged optimized PPI treatment for any GERD indication during a consecutive 4 week period. (An optimized PPI treatment is a treatment, which according to the investigator's judgment cannot be further improved by changing brand or dosing of the PPI).
    c. Patients with a history of reflux (erosive) esophagitis Los Angeles grade A-D must have been treated with a PPI during a consecutive 8 week period (with optimized PPI treatment during at least a consecutive 4 week period).
    d. Remaining GERD symptoms despite optimized PPI treatment.

5. To be eligible for enrolment, the patients had to report, in the RESQ-7 screening instrument using 7 days recall one or both of the following:
    a. A minimum of 3 days of a burning feeling behind the breastbone of at least moderate intensity

b. A minimum of at least 3 days of an unpleasant movement of material upwards from the stomach of at least moderate intensity.

Exclusion Criteria

1. Patients that had not experienced any GERD symptom improvement at all during PPI treatment.
2. Any other condition which in the opinion of the investigator rendered the patient unsuitable for inclusion in the study.
3. Involvement in the planning or conduct of the study.
4. Previous enrolment in the present study.
5. Involvement in any other observational study or in any clinical study at the time of this study or during the last 6 months

RESULTS:

Patient characteristics

Number of patients in the study, at

- Baseline, n=552
- 3 months follow up, n=451
- 6 months follow up, n=404

Patient characteristics at baseline

Mean age: 54.7 years (SD 14.4)
Female: 70.3%
Mean BMI: 31.5 (which falls into the obese category) (SD 7.7)
Medical history:

- Dyspeptic symptoms: 55%
- IBS: 17%
- Hiatal hernia: 32%
- Erosive esophagitis: 14%

Resource utilization data

Nr of patients receiving each Test or Procedure at least once

	6 months prior to baseline to baseline visit (n=552)	Month 1-3 follow up (n=451)	Month 4-6 follow up (n=404)
Endoscopy	47%	25%	15%
Blood sample for laboratory tests	19%	-	-
ECG	12%	-	-
Radiological examination	11%	-	-
Upper abdominal ultrasound	8%	-	-
Manometry	1%	-	-
24-hr pH monitoring	1%	-	-
Bernstein test	0.4%	-	-
Acid perfusion	-	2%	2%
Dilatation of stricture	-	7%	6%
Esophageal motility study	-	5%	3%

Endoscopy findings from 6 months prior to baseline to baseline visit (n=552):

Hitatus hernia: 41%
Barrett's oesophagus: 13%
Stomach ulcer(s): 12%
Mucosal breaks: 13%
Esophageal stricture: 6%
Duodenum ulcer(s): 2%
Esophagitis (reported as "Other abnormal findings"): 5%

GERD medication (ATC code A02B), at baseline and after 6 months follow up

- High dose PPI without adjunctive therapy: 43% of patients at baseline and 38% at 6 months follow up
- Standard dose PPI without adjunctive therapy: 37% of patients at baseline and 18% at 6 months follow up
- Other medication (with or without PPI): 18% of patients at baseline and 19% at 6 months follow up. (Other medication was most often used as adjunctive treatment to PPIs and the most common "Other medication" was H2RAs (35% of "Other medication" was H2RAs.))

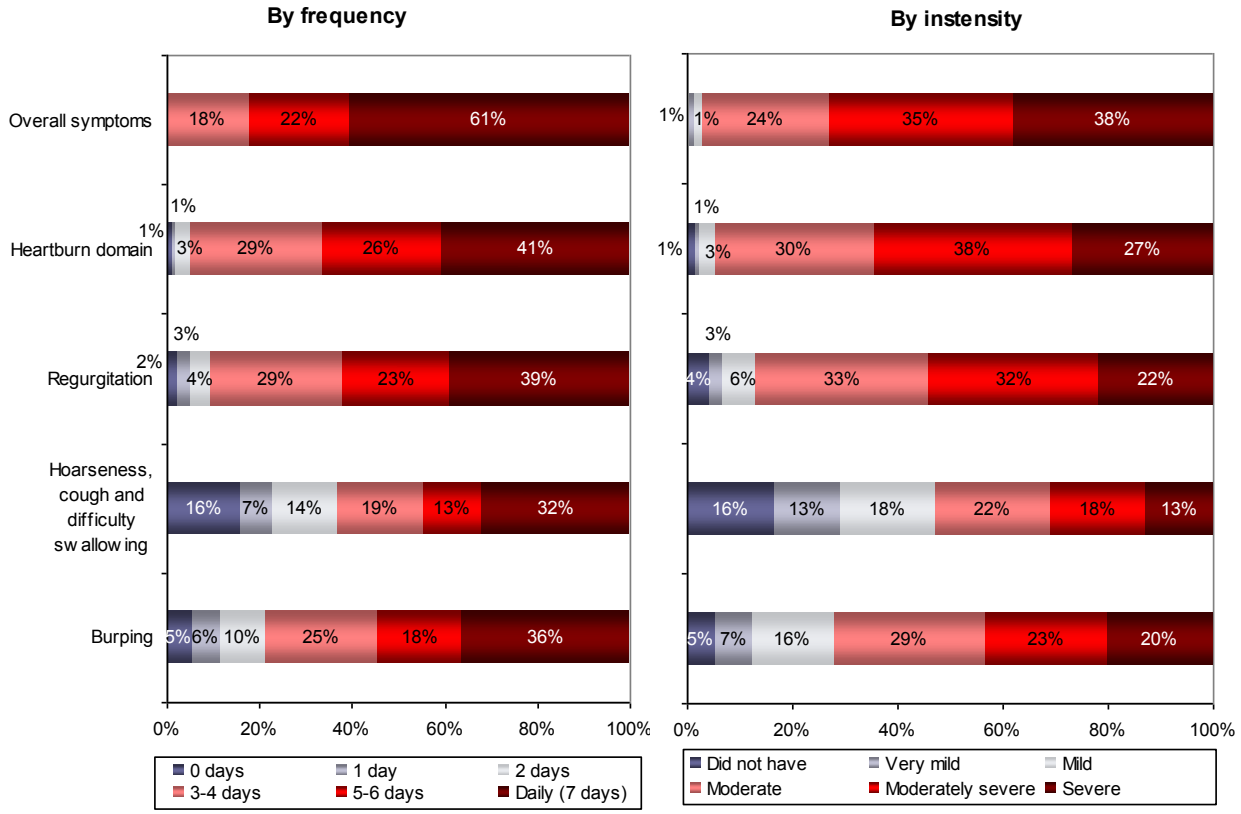
Nr of patients with Medical visits and Hospitalizations due to GERD-related conditions:

6 months prior to baseline to baseline visit	Month 1-3 follow up	Month 4-6 follow up
(n=552)	(n=451)	(n=404)
Primary care visits	283 (51%)	235 (52%)	168 (42%)
Gastroenterologist visits	245 (44%)	156 (35%)	101 (25%)
Emergency room visits	35 (6%)	37 (8%)	28 (7%)
Hospitalizations	16 (3%)	58 (13%)	40 (10%)

Patient's symptom load (at baseline, 3 and 6 months follow-up)

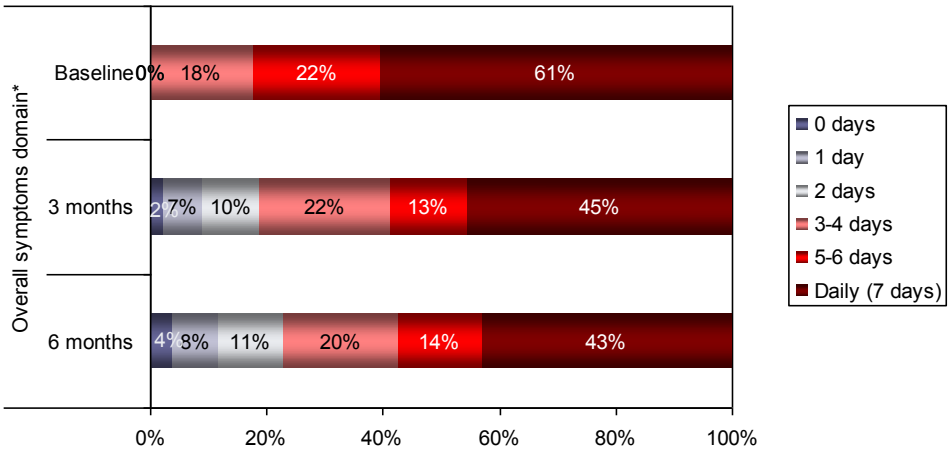
Patients had a high symptom-load at baseline (consistent with study inclusion criteria), measured by RESQ-7. As expected due to the fluctuating nature of the disease, the symptom load was not as high at 3 months and 6 months follow-up.

Figure 1. Symptom frequency (number of days over past 7 days) and symptom intensity (over past 7 days) of RESQ-7 domains* at baseline



* For each patient, the item(s) considered was/were the item(s) within the domain with the highest frequency.

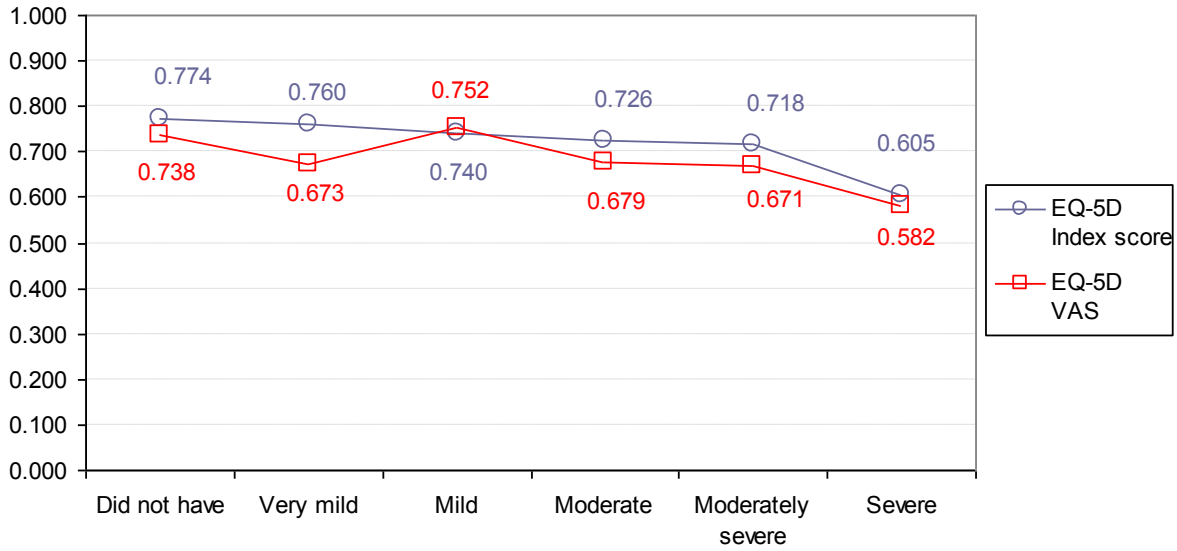
Figure 2. Frequency (number of days over past 7 days) of Overall symptoms domain* at baseline, 3 months and 6 months follow-up



* For each patient, the item(s) considered was/were the item(s) within the domain with the highest frequency.

Health-related quality of life and Productivity loss (at baseline and 6 months after baseline)
Patients reported impairment in HRQL (measured by, for example EQ-5D and QOLRAD-RI, see Figure 3 and Table 2), and in productivity (measured by WPAI-GERD), particularly at baseline.

Figure 3. Mean EQ-5D Index Scores and VAS by intensity of RESQ-7 Heartburn domain symptoms* at baseline.



* For each patient, the item(s) considered was/were the item(s) within the domain with the highest frequency.

Table 2. QOLRAD-RI domains*: Descriptive statistics at baseline (n=552)

	n	Mean	95% CI
Emotional distress	546	4.19	4.06; 4.32
Sleep disturbance	546	3.89	3.76; 4.02
Food/drink problems	548	3.46	3.35; 3.57
Physical/social Functioning	548	4.71	4.58; 4.83
Vitality	547	3.77	3.66; 3.89

* Domain range 1-7, with low scores indicating a more severe impairment of daily functioning.

Cost per patient

- The yearly total cost per patient among partial responders to PPI treatment was estimated to be $9,944 (41% direct medical costs, 59% productivity losses).
- High symptom load was associated with lower HRQL and productivity and higher total direct costs.

Cost of illness

The cost of illness of partial responders to PPI treatment among patients with GERD in the US adult population ranged from $13.5 to $21 billion per year. The direct cost of illness is comparable to the overall patients with GERD, and much lower compared with diabetes or cardiovascular disease.

Treatment pathways

- Chronological ranking analysis of Tests and Procedures showed that ECG (resting/exercise) was ranked to be performed first, followed by blood sample for laboratory tests and then upper gastrointestinal endoscopy. These were then followed by Imaging (radiological examination/upper abdominal ultrasound) and 24-hr pH monitoring.
- Probability trees showed that the most common medication category was treatment with high dose PPI without adjunctive therapy (43%), followed by standard dose PPI without adjunctive therapy (37%).
- Minor trends could be perceived regarding differences between some medication categories in resource utilization, HRQL and/or productivity. However, the sample size in those categories was much too small to draw any valid conclusions.
- Overall, it was difficult to arrive at a typical treatment pathway for these patients. But it was seen that patients do not change medication categories frequently. A potential explanation could be that there currently is no clear treatment alternative available in clinical practice for the patient group, other than continued PPI treatment.

Proportion of partial responders to PPI therapy among all patients with GERD

The estimation of partial responders to PPI out of the total GERD population ranged from 9.7% to 15.2%.