Clinical Study Report Synopsis	
Drug Substance	NA
Study Code	NIS-GGR-DUM-2009/1
Edition Number	3.0 (Final)
Date	05 May 2010

TITLE
A CROSS-SECTIONAL STUDY ON THE PREVALENCE AND IMPACT IN WORK PRODUCTIVITY OF GERD IN PRIMARY CARE PATIENTS WITH UPPER GI SYMPTOMS USING THE NOVEL QUESTIONNAIRE GERD-Q. THE GREEK GERD-Q STUDY

Study dates: First patient enrolled: 08 Jul 2009
Last patient completed: 10 Dec 2009

Phase of development: NA (Observational NIS study)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
CI	Confidence Interval
GERD	Gastroesophageal Reflux Disease
GerdQ	Gastroesophageal Reflux Disease Questionnaire
GP	General Practitioner
GI	Gastrointestinal
H_2RAs	H_2 Receptor-Antagonists
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NA	Not Available
OR	Odds Ratio
PPIs	Proton Pump Inhibitors
WPAI - GERD	Work Productivity and Activity Impairment questionnaire – Gastroesophageal Reflux Disease
WPS	Work Productivity Score

Study centre(s)

Ninety one (91) primary care office-based physicians (GPs)

Publications

Not applicable

Objectives

Primary

- To provide data on GERD prevalence in primary care subjects with upper GI symptoms using the novel GerdQ questionnaire.

Secondary

- To estimate GERD prevalence based on patients' symptoms as reported to their physicians.
- To observe possible variations between the two methods (physicians' symptom rating and GerdQ questionnaire).
- To record any potential antisecretory treatment and to identify the percentage of patients that may require change of their treatment based on GerdQ questionnaire.
- To describe the impact of GERD symptoms on productivity and its potential impact in the Greek economic setting.

Study design

Epidemiological, cross-sectional, single visit study.

Target patient population and sample size

Adult patients (≥18 years) with upper GI symptoms the last week prior to the study visit, who consented for study participation, and were willing to complete at maximum 2 questionnaires, were consecutively enrolled by the participating GPs. Reasons for exclusion from the study were history of oesophageal/gastroduodenal surgery, history of malignant disease, treatment with Aspirin/NSAIDs the last week prior to study visit and PPI treatment for eradication of *Helicobacter Pylori* or for healing of peptic ulcer caused by NSAIDs.

Although 950 patients were planned to be recruited in the present study, 889 patients were finally enrolled. Two male patients were identified as protocol violators (the first due to history of prostate cancer and the second due to history of cancerous intestine). Protocol violators were not included in the statistical analysis.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Not applicable

Duration of treatment

Not applicable

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary end point

- Percentage of patients with GERD (GerdQ score ≥ 8)

Secondary endpoints

- Percentage of patients with GERD based on reported symptoms (heartburn and/or regurgitation ≥ 2 days/week)
- Percentage of patients with antisecretory treatment and type of treatment
- Percentage of patients who may need change of their antisecretory treatment (assessed with GerdQ questionnaire)
- Productivity (WPAI-GERD score)
- Number of physician visits due to GERD

Patient-reported outcomes (PROs)

The GerdQ questionnaire was completed by all participating patients. Those who scored ≥ 8 were also asked to complete the WPAI-GERD questionnaire in order to assess the productivity in work and in daily activities.

Criteria for evaluation - safety

No safety data were collected in the present study. Participating investigators were required to report adverse reactions according to national requirements for post-marketing reporting.

Statistical methods

Statistical analysis was based on the evaluable population (N=887). Descriptive statistical methodology was applied to explore the distribution of study variables. The association between categorical variables of interest was evaluated with Pearson's chi square test whereas the magnitude of association was based on the respective odds ratio (OR).

Summary of results

Patients' demographics and baseline characteristics

Eight hundred and eighty seven (887) patients with mean age of 51.2±17.0 years were analyzed in the present study. Demographics and baseline characteristics are presented in table 1.

Table 1. Patients' demographics and baseline characteristics

		Mean	SD
Age (yrs)		51.2	17.0
BMI (kg/m^2**)**		26.5	3.9
		N	**%**
Sex	Male	414	46.7
	Female	473	53.7
Employment status	Employed	506	57.5
	Retired	218	24.6
	Domestic duties	114	12.9
	Unemployed	30	3.4
	Student	8	0.9
	Sick leave	1	0.1
	Permanent handicap	1	0.1
	Other	2	0.2
	NA	7	
Educational Level	No education	6	0.7
	Primary	138	15.7
	Lower Secondary	108	12.3
	Higher Secondary	254	29.0
	Technological Institute	132	15.1
	University	239	27.3
	Total	877	100.0
	NA	10	

General medical history and history of GI tract disorders

Four hundred and seventy nine patients (54% of the study population) had negative medical history. Arterial hypertension followed by diabetes mellitus, respiratory diseases, cardiovascular diseases and dyslipidemia were the most prevalent co-morbidities (table 2).

Table 2. Patients' medical history

	N	%
Arterial hypertension	265	29.9%
Diabetes Mellitus	96	10.8%
Cardiovascular Diseases	74	8.3%
Respiratory Diseases	72	8.1%
Dyslipidemia	52	5.9%
Endocrine/Metabolic disorders	36	4.1%
Musculoskeletal and connective tissue disorders	25	2.8%
Central Nervous System Disorders	24	2.7%
Immune system disorders	7	0.8%
Renal disorders	4	0.5%
Benign prostate hyperplasia	3	0.3%
Hematological disorders	3	0.3%
Other	3	0.3%

The majority of patients had a history of at least one GI tract disorder (554/887, 62.5%) whereas the most frequent disorders (>10% of the study population) were GERD with or without oesophagitis, and gastritis/duodenitis, as shown in table 3.

Table 3. Patients' history of GI tract disorders

	N	%
GERD	383	43.2
Gastritis/Duodenitis	156	17.6
Oesophagitis	107	12.1
Hiatus hernia	57	6.4
Duodenal ulcer	35	3.9
Gastric ulcer	9	1.0
Irritable bowel syndrome	5	0.6
Diverticulitis	4	0.5
Constipation	3	0.3
Cholecystectomy	3	0.3
Dyspepsia	3	0.3
Other	12	1.4

Upper GI symptoms

Heartburn and acid regurgitation were the most frequent upper GI symptoms reported by the patients during the last 7 days prior to study visit. The reported upper GI symptoms were of mild-to-moderate intensity in most cases. (table 4).

Table 4. Upper GI symptoms reported during the week prior to study visit

		Frequency of Symptoms				Intensity		
		Absent	**1 day**	**≥2 days**	**Every day**	**Mild**	**Moderate**	**Severe**
Heartburn	**N**	113	221	399	154	278	402	94
	%	12.7	24.9	45.0	17.4	35.9	51.9	12.1
Regurgitation	**N**	180	291	312	104	298	336	72
	%	20.3	32.8	35.2	11.7	42.2	47.6	10.2
Epigastric pain	**N**	300	255	278	54	291	239	57
	%	33.8	28.7	31.3	6.1	49.6	40.7	9.7
Early satiety	**N**	492	187	151	57	234	127	33
	%	55.5	21.1	17.0	6.4	59.4	32.2	8.4
Postprandial fullness	**N**	333	210	235	109	299	201	52
	%	37.5	23.7	26.5	12.3	54.2	36.4	9.4
Nausea	**N**	536	192	141	18	228	110	12
	%	60.4	21.6	15.9	2.0	65.1	31.4	3.4
Vomiting	**N**	776	87	23	1	70	36	5
	%	87.5	9.8	2.6	0.1	63.1	32.4	4.5
Bloating	**N**	398	204	221	64	249	205	34
	%	44.9	23.0	24.9	7.2	51.0	42.0	7.0
Belching	**N**	224	218	322	123	278	308	77
	%	25.3	24.6	36.3	13.9	41.9	46.5	11.6

Prevalence of GERD

Prevalence of GERD was assessed with the use of the GerdQ questionnaire. Patients with a total GerdQ score ≥ 8 were considered as having GERD, whereas those with a score of 0-7 were considered as having a low probability of GERD. Overall, 71.8% (637/887) of the study population was considered as suffering from GERD (table 5).

Table 5. Patients presenting with GERD according to GerdQ questionnaire

	Total GerdQ Score	**N**	**%**
Presence of GERD	**No**	**250**	**28.2**
	0-2	7	0.8
	3-7	243	27.4
	Yes	**637**	**71.8**
	8-10	363	40.9
	11-18	274	30.9

Out of the 637 patients with total GerdQ score ≥8, 350 (54.9%) patients were considered as having inconvenient GERD (impact score <3) whereas 287 (45.1%) were experiencing disrupting GERD (impact score ≥3), as shown in table 6.

Table 6. GERD patients presenting with inconvenient or disrupting GERD

	GerdQ Score	Impact Score	Diagnosis	N	%
Presence of GERD	**8-10**	**<3**	Inconvenient GERD	279	43.8
		≥3	Disrupting GERD	84	13.2
	11-18	**<3**	Inconvenient GERD	71	11.2
		≥3	Disrupting GERD	203	31.8

Prevalence of GERD was also assessed on the basis of reported symptoms and taking as a cut-off point a frequency of ≥2 days/week for heartburn and/or regurgitation. According to this, it was estimated that 70.7% (627/887) of the study population was suffering from GERD at the time of the study visit.

GerdQ Score ≥ 8 was significantly associated with history of GI tract disorders. Specifically, history of GI tract disorders was associated with 1.6 times fold increase of the possibility of having GerdQ score ≥ 8 (95% CI: 1.19-2.15, p=0.002). This was mainly resulted due to the strong positive association between history of GERD and GerdQ score ≥8, (OR: 2.08, 95% CI: 1.52-2.83, p<0.001) as shown in table 7.

Table 7. Association of GerdQ score with history of GI tract disorders

		GerdQ Score ≥8	p-value	OR	95% CI
Presence of GI tract disorders	**Yes**	418/554 (75.5%)	0.002	1.60	1.19-2.15
	No	219/333 (65.8%)			
History GERD	**Yes**	306/383 (79.9%)	<0.001	2.08	1.52-2.83
	No	331/504 (65.7%)			

Antisecretory treatment

At the time of the study visit and during the last month 553 patients (62.3%) were treated for upper GI symptoms. Most of the patients were receiving antacids (N=395, 44.5%), followed by PPIs (N=250, 28.2%), H_2RAs (N=139, 15.7%), and prokinetics (N=56, 6.3%), either as monotherapy or combinations, (Figure 1, Table 8).

Figure 1. Antisecretory treatment for upper GI symptoms

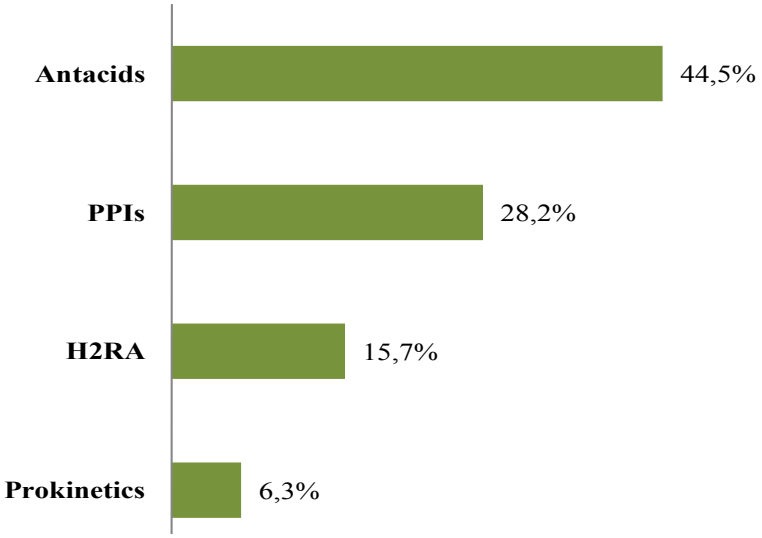

Table 8. Detailed antisecretory treatment for upper GI symptoms

	N	%
Antacids	173	19.5
PPIs & Antacids	101	11.4
PPIs	93	10.5
H_2RA & Antacids	81	9.1
H_2RA	33	3.7
PPIs & Antacids & Prokinetics	20	2.3
PPIs & Prokinetics	18	2.0
PPIs & H_2RA & Antacids	9	1.0
PPIs & H_2RA	7	0.8
Antacids & Prokinetics	6	0.7
H_2RA & Antacids & Prokinetics	5	0.6
Prokinetics	3	0.3
PPIs & H_2RA & Prokinetics	2	0.2
H_2RA & Prokinetics	2	0.2

Patients treated with PPI-based therapy received mainly conventional PPIs doses (96.8%), whereas on demand administration was reported by 67.6% of the study population (table 9).

The highest treatment compliance (“received all doses”) among the 81 patients on continuous PPI therapy was observed in 48 patients (59.3%) while 23 patients (28.4%) reported that they miss doses more than once per week (lowest compliance) as shown in table 9.

Table 9. Dose administration and compliance of patients receiving PPI-based therapy

	N	%
PPI dose		
Conventional dose	242	96.8
High dose	8	3.2
Administration		
On demand	169	67.6
Continuous	81	32.4
Compliance (if continuous)*		
>1 per week	23	28.4
1 per week	4	4.9
1 every 2 weeks	3	3.7
1 per month or less	3	3.7
Received all doses	48	59.3

** Refers to doses missed*

Almost all patients treated with H_2RA-based therapy were receiving treatment on demand (94.9%). Only 7 patients were receiving continuous treatment and 3 did not miss any dose, (table 10).

Table 10. Dose administration and compliance of patients receiving H_2RA-based therapy

	N	%
Treatment		
On demand	131	94.9
Continuous	7	5.1
Compliance (if continuous)*		
>1 per week	2	28.6
1 per week	1	14.3
1 every 2 weeks	0	0.0
1 per month or less	1	14.3
Received all doses	3	42.9

** Refers to doses missed*

Prevalence of GERD in naïve patients

In patients not receiving any antisecretory treatment (N=334) at the time of the study visit (naive patients), GERD (total GerdQ score ≥8) was diagnosed in 221 patients (66.2%) as reported in table 11. In these patients, the GerdQ impact score indicated inconvenient GERD in 85.1% of patients (Table 12).

Table 11: GERD score in naïve patients

			N	%
Presence of GERD	**No**		113	33.8
		0-2	2	0.6
		3-7	111	33.2
	Yes		221	66.2
		8-10	162	48.5
		11-18	59	17.7

Table 12: GerdQ impact score in naïve GERD patients

	N	%
Inconvenient GERD (<3)	188	85.1
Disrupting GERD (≥3)	33	14.9
Total	221	100.0

Patients that may potentially require change of their antisecretory treatment

Response to treatment and therefore potential need for change of antiscretory therapy was assessed with the GerdQ questionnaire. Patients with a frequency of heartburn and/or regurgitation for ≥2 days/week, and/or with sleeping difficulties due to heartburn/ regurgitation or additional OTC treatment receipt due to heartburn/regurgitation for ≥2 days/week, were considered as non-responders and in a potential need of antisecretory treatment modification. At the time of the study visit 84.8% were considered as non-responders and are potential candidates for modification of their current antisecretory therapy (table 13).

Table 13. Response to treatment according to GerdQ questionnaire

Response to Treatment		
No	**Yes**	**Total**
469 (84.8%)	84 (15.2%)	553

In the subgroup of patients with GerdQ score ≥8, the percentage of patients who would potentially need change of antisecretory treatment was even higher reaching 94% of them (table 14).

Table 14. Response to treatment in the subgroup of patients with GerdQ score ≥8

Response to Treatment		
No	**Yes**	**Total**
391 (93.9%)	25 (6.1%)	416

Finally, in the subgroup of PPI treated GERD patients, the percentage of patient who would potentially need change in the treatment was not significantly different by administration type (on demand vs. continuously), as shown in table 15.

Table 15. Response to PPIs in patients with GERDQ ≥8 by type of administration

PPI treatment	Non-Responders N (%)	Responders N (%)	Total
On demand	127 (95.4)	6 (4.5)	133
Continuously	55 (93.2)	4 (6.8)	59
Total	**182**	**10**	**192**

p=0.764

Impact of GERD in work productivity and activity impairment plus relative economic impact

Impact of GERD in working productivity and activity impairment was assessed with the WPAI-GERD questionnaire which was completed only by patients with total GerdQ score of ≥8 (637). 635 patients completed the WPAI-GERD questionnaire and 350 participants were employed at the time of the study. Among these patients, the mean hours absent from work were 2.3±4.9 (absenteeism) whereas the percent reduced productivity while at work was 32.1±21.9%. The number of lost working hours due to reduced productivity (presenteeism) was 11.8±9.6 and the percent work time missed due to GERD was estimated as 6.9±14.9%**.** Productivity reduction in daily activities was estimated to be 37.4±23.1%. The WPS was 34.6 ± 25.2 (table 16).

Table 16. WPAI-GERD productivity scores

	Hours absent from work	% reduced productivity while at work 100	% reduced productivity while carrying out daily activities	No of work hours lost due to reduced productivity	% of work time missed due to GERD	WPS
N	350	331	633	347	338	349
Mean±SD	2.3±4.9	32.1±21.9%	37.4±23.1%	11.8±9.6	6.9±14.9%	34.6±25.2
Median	0	30%	30%	10.5	0%	30%
Range	[0-50]	[0%-90%]	[0%-100%]	[0-68]	[0%-100%]	[0%-100%]

The impact of work loss in monetary values was 34.8±73.4€ regarding hours absent from work (absenteeism) and 176.6±143.4€ with respect to work hours lost due to reduced productivity (presenteeism), as shown in table 17.

Table 17. Monetary values

	Monetary values* hours absent (€)	Work hours lost due to reduced productivity (€)	Hours absent + work hours lost due to reduced productivity (€)
N	350	347	347
Mean±SD	34.8±73.4	176.6±143.4	211.6±173.3
Median	73.4	157.5	180
Range	[0-750]	[0-1020]	[0-1110]

***The hourly working fee was assumed at 15€ (based on latest Eurostat data for Greece)**
http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tps00173&plugin=0

Health care recourse utilization

Utilization of any of health care recourses, defined as: "visit for any reason to a medical center" was reported for 61.8% of the study population (524/848). This number did not vary significantly when only patients with GerdQ ≥8 were considered: 63.4% (390/615), (table 18).

Table 18. Health care recourse utilization

	Total Study Population N (%)	Patients with GerdQ≥8 N (%)
At least one visit for any reason to medical centre	524 (61.8)	390 (63.4)
No visits at any medical centre	324 (38.2)	225 (36.6)
Total	848 (100)	615 (100)

Health care resource utilization in more details is shown in table 19. Almost 32% of the patients visited at least once a primary health care physician during the last 6 months due to GERD; this number is slightly increased to 36.1% in patients with GerdQ score ≥8. The same trend stands for visits to any health recourses (table 19).

Table 19. Detailed health care resource utilization

		Total Study Population		Patients with GerdQ≥8	
		Patients with at least one visit (any reason) N (%)	Patients with at least one GERD related visit N (%)	Patients with at least one visit (any reason) N (%)	Patients with at least one GERD related visit N (%)
Primary care visits	**Yes**	431 (51.7)	262 (31.8)	313 (51.9)	216 (36.1)
	No	402 (48.3)	561 (68.2)	290 (48.1)	383 (63.9)
	Total	833	823	603	599
Visits to Gastroenterologist	**Yes**	144 (17.7)	113 (13.9)	119 (20.0)	98 (16.5)
	No	671 (82.3)	700 (86.1)	476 (80.0)	496 (83.5)
	Total	815	813	595	594
Visits to other specialists	**Yes**	132 (16.4)	44 (5.5)	110 (18.7)	40 (6.8)
	No	672 (83.6)	757 (94.5)	478 (81.3)	545 (93.2)
	Total	804	801	588	585
Visits to outpatient departments	**Yes**	50 (6.1)	18 (2.2)	42 (7.1)	17 (2.9)
	No	766 (93.9)	797 (97.8)	553 (92.9)	578 (97.1)
	Total	816	816	595	595
Hospitalizations (days)	**Yes**	10 (1.2)	4 (0.5)	10 (1.7)	4 (0.7)
	No	806 (98.8)	812 (99.5)	585 (98.3)	591 (99.3)
	Total	816	816	595	595

As illustrated in Table 20, 36.7% of the visits in primary care facilities were GERD-related. This number was slightly increased to 41.6% in patients with GerdQ score ≥8. The majority of visits to gastroenterologists were performed for GERD-related reasons (79.6%). As expected, this number was not significantly different in patients with GerdQ score ≥8 (80.6%). No differences were observed between the total study population and the subgroup of patients with GerdQ score ≥8 with respect to the number of visits to other specialists, outpatient clinics and number of hospitalization days due to GERD.

Table 20. Total number of visits to health resources

		Sum of visits due to any reason	Sum of GERD related visits	% of GERD related visits
Primary care visits	**Total Population**	1515	556	36.7%
	GerdQ≥8	1139	474	41.6%
Visits to Gastroenterologists	**Total Population**	181	144	79.6%
	GerdQ≥8	155	128	80.6%
Visits to other specialists	**Total Population**	360	76	21.1%
	GerdQ≥8	290	72	24.8%
Visits to outpatient departments	**Total Population**	86	25	29.1%
	GerdQ ≥8	76	24	31.6%
Days of hospitalization	**Total Population**	50	8	16.0%
	GerdQ ≥8	50	8	16.0%

Summary of pharmacokinetic results
Not applicable

Summary of pharmacodynamic results
Not applicable

Summary of pharmacokinetic/pharmacodynamic relationships
Not applicable

Summary of pharmacogenetic results
Not applicable

Summary of safety results
Not applicable

Study Code: NIS-GGR-DUM-2009/1

Version: 3.0 (Final)

Date : 05 May 2010

Synopsis Clinical Study Report (CSR) – Signature Page

MC SDL

Date

By

Signature

Name

Title

MC Medical Officer

Date

By

Signature

Name

Title