Observational Protocol:

Partial Response to PPI-treatment: the Cost to Society and the Burden to the Patient

REMAIN - France

Version: 1.1

Final:

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1 PROTOCOL SYNOPSIS

Title	Partial Responders to PPI treatment: the Cost to Society and the Burden to the Patient – a study in France (REMAIN Study –French Arm)
Protocol Number	Study code D9120N00013
Study design	French arm of a multi-center, prospective, observational, non interventional study
Patients	Patients with Gastroesophageal Reflux Disease (GERD) newly classified as partial-responders to proton pump inhibitors (PPIs)
Period for Patient Participation	
Primary objectives	– To describe common treatment pathways, including extent of and time to referral to specialists; – To collect resource utilization data; – To collect relevant cost estimates and calculate cost per patient; – To assess the symptom load, impact of symptoms on daily life and effect on work productivity.
Secondary objectives	– To estimate the proportion of new partial-responders to all new patients with GERD
Inclusion criteria	1. Provision of signed informed consent. 2. Able to read and write in French and able to comply with study requirements. 3. Female or male, aged 18 years or above. 4. The patient must at the enrolment visit be identified for the first time as partial responder to PPI treatment as defined by the following criteria: a) At least 6 month history of GERD symptoms (need not be consecutive) b) Continuously treated with unchanged optimized PPI treatment for any GERD indication during the last 4 weeks (an optimized PPI treatment is a treatment, which according to the investigators 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 continuously treated with a PPI during the last 8 weeks before enrolment (optimized PPI treatment during the last 4 weeks before enrolment).

	5. To be eligible for enrolment, the patients must have reported, in the RDQ-RI screening instrument using 7 days recall, a minimum of three days with at least one of the two following symptoms with at least moderate severity: • a burning feeling behind the breastbone • an unpleasant movement of material upwards from the stomach.
Exclusion criteria	1. Patients that have not experienced any GERD symptoms improvement at all during PPI treatment. 2. Prior surgery of the upper GI tract (open, endoscopic and laparoscopic surgery on the esophagus, the stomach and the duodenum with the exception of over sewing or endoscopic treatment of an bleeding ulcer) 3. Any other condition which in the opinion of the investigator would render the patient unsuitable for inclusion in the study. 4. Involvement in the planning or conduct of the study. 5. Previous enrolment in the present study. 6. Involvement in any other observational study or in any clinical study at the time of this study or during the last 6 months.
Primary and secondary endpoints	Frequency and severity of GERD symptoms Quality of Life Productivity loss Healthcare resource use (primary care visits, secondary care visits, medications, diagnostic tests, surgeries, etc.) Utility values
Patient-reported Outcome Instruments	Reflux Disease Questionnaire – Reflux Inhibition (RDQ-RI) GERDQ Quality of Life in Reflux and Dyspepsia – Reflux Inhibition (QOLRAD-RI) EQ-5D Short Form 36 (v2) HADS Work Productivity and Activity Impairment for Patients with Gastroesophageal Reflux Disease (WPAI-GERD) Resource Utilization Questionnaire
Sample size	275 enrolled partial-responders to PPI for the treatment of GERD (200 completed subjects)
Procedures	Patients will be recruited by their physicians during a regularly scheduled office visit. The physician will recruit patients into the study who are

	identified for the first time as partial responders to PPI treatment. Patients will be asked to complete a self-administered questionnaire at the recruitment visit and every 3 months for a total period of 12 months thereafter. Follow-up questionnaires will be sent to the patient's place of residence. Physicians will collect the patient's medical history, demographics and co morbidities in a paper CRF at the recruitment visit and will collect information from medical records on health resource use every 6 months for a total of 12 months per patient. In addition, the physician will keep a log of all new patients with GERD seen at their office during the enrollment period in order to allow for an estimate of the ratio of partial responders to all new patients with GERD.
Statistical considerations	Due to the descriptive objectives of the study, there are no hypotheses to test with statistical methods to predetermine a required sample size. The choice of target sample is therefore pragmatic guided mainly by sample sizes in previous similar studies

Study glossary

AZ	AstraZeneca R&D, Mölndal, Sweden
CRF	Case Report Form
CNIL	Commission Nationale Informatique et Liberté
CNOM	Conseil National de l'Ordre des Médécins
CCTIRS	Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GERD	Gastro Esophageal Reflux Disease
GERDQ	Questionnaire for patients with symptoms in the upper gastrointestinal tract
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ICH	International Code of Harmonization
ISF	Investigator Study File
PCP	Primary Care Physician
PPIs	Proton Pump Inhibitors
PRO	Patient Reported Outcomes
QOLRAD-RI	Quality of Life in Reflux and Dyspepsia – Reflux Inhibition
RDQ-RI	Reflux Disease Questionnaire – Reflux Inhibition
SAE	Serious Adverse Event
SF-36	Short Form 36
SOP	Standard Operating Procedures
TLESR	Transient Lower Esophageal Sphincter Relaxation
WPAI-GERD	Work Productivity and Activity Impairment – Gastro-Esophageal Reflux Disease

2 BACKGROUND AND RATIONALE

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders worldwide. It is estimated that approximately 20% of the Western population suffers from GERD symptoms at least weekly[1], but this figure may underestimate the true prevalence, since many patients self-medicate and do not seek medical attention.[2] Others are not aware that they have GERD.[3] According to Bardhan *et al*[4] the mean age of patients at presentation with GERD is 53.5, with a slight preponderance among males (55% vs. 45%).

GERD is characterized by reflux of the stomach contents into the esophagus, oropharynx, larynx, or airway. The primary etiology is transient lower esophageal sphincter relaxation (TLESR), however, other mechanisms may include decreased LES resting pressure, impaired esophageal clearance, delayed gastric emptying, decreased salivation, or impaired tissue resistance[5].

Symptoms of GERD include heartburn, regurgitation, and dysphagia, as well as extra-esophageal or atypical manifestations such as cough, asthma, laryngitis, or non-cardiac chest pain[6]. Potentially serious esophageal complications can include esophagitis, esophageal ulcers, esophageal stricture or obstruction, Barrett's esophagus or esophageal cancer, as well as extra-esophageal diseases such as respiratory problems, chest pain, angina, and increased mortality in the year after diagnosis.[7] In addition to the physical ramifications of the disease, GERD sufferers report significant treatment burden and negative impact of the disease on quality of life. [8]

The diagnosis of GERD is often made subjectively when symptoms respond to acid suppressive therapy[9] with H-2 receptor antagonists, or proton pump inhibitors (PPIs), though additional confirmatory diagnostic tests include 24-hour pH monitoring, endoscopy, biopsy, barium swallow, laryngoscopy, and esophageal motility testing. Endoscopy is the gold standard to definitively diagnose erosive esophagitis.

PPIs and Partial Response

Therapy with a PPI is currently considered the most effective way to relieve symptoms and to help promote esophageal healing in GERD. Since GERD is a chronic disease that often relapses, long-term maintenance therapy with a PPI is usually necessary[10]; however, some patients continue to experience symptoms despite PPI therapy.[11]

Non-acid reflux has been identified as one of the causes of persistent symptoms despite PPI therapy and it is estimated that weakly or non-acidic reflux episodes play a major role in eliciting symptoms in 30-40% of patients on PPI therapy. It is for this reason medications that inhibit TLESR (e.g., baclofen) can be used as a therapeutic option; however, its use is limited due to side effects[12]. There are also anti-reflux surgical procedures that tighten the lower esophageal

sphincter and inhibit TLESR (e.g., fundoplication, endoscopic Stretta procedure), but the benefits are limited by the costs,[14] surgical risks,[15] and, at times, long term efficacy[16].

Health-related quality of life on medication remains significantly impaired in partial-responders compared to good responders, as measured with both generic and health-specific questionnaires.[17] In addition, information concerning the frequency and severity of symptoms in this group of patients is limited, and there are currently no guidelines available for treatment.

Because of this lack of research studies on the burden of illness to partial-responders, results from this observational cost and burden of illness study in PPI partial-responders is expected to provide important empirical data to support further knowledge about this patient population.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives of this observational, prospective study are

- to describe common treatment pathways, including extent of and time to referral to specialists
- to collect resource utilization data
- to collect relevant cost estimates and to calculate the cost per patient
- to assess the symptom load, impact of symptoms on daily life and effect on work productivity
- to assess the effect of partial response on HRQoL

in patients with GERD newly identified as partial responders to PPI treatment.

3.2 Secondary Objective

The secondary objective of this study is to estimate the proportion of patients with GERD being identified for the first time as partial responders to optimized PPI treatment, to all patients newly diagnosed with GERD.

4 STUDY DESIGN OVERVIEW

This is a multi-center, 12 months prospective study in France. Approximately 275 adult (18 years or older) patients with GERD who have been identified for the first time as partial responders to optimized PPI treatment will be enrolled at approximately 30 sites in France to obtain an evaluable target sample size of 200 patients, assuming an estimated 30% attrition rate over the course of the study.

Patients will be enrolled at a regularly scheduled office visit. At this regularly scheduled office visit, the study physician or designated staff will invite potentially eligible patients to participate in the study. Patients will be provided with a written study description and copy of the informed consent form to review. Eligible patients who express an interest in participating will be officially enrolled in the study on the day of the office visit.

Enrolled patients will fill out a self-administered paper patient survey during this visit including questions for their quality of life and symptoms severity.

Physicians will complete the enrollment part of the CRF including patient demographics and confirmation of patient's eligibility. They will also keep a log of all newly diagnosed patients with

GERD seen during the enrollment period in order to provide estimates of the ratio of patients with GERD identified for the first time as partial responders to optimized PPI treatment to all newly diagnosed patients with GERD. The physician will follow the patients through a period of 12 months after enrollment collecting data from the patient medical records at baseline, month 6 and month 12.

The patient will receive a set of questionnaires every 3 months during the same 12 month period after the first visit. This survey will include questions relating to resource utilization (over the counter medication and visits to other physicians), as well as questionnaires relating to the patient's quality of life and symptom frequency and severity.

5 SUBJECT POPULATION

The target population for this study is adults, aged 18 and older, who are suffering from GERD and are newly diagnosed as partial responder to optimized PPI treatment. Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Inclusion Criteria:

1. Provision of signed informed consent.
2. Able to read and write in French and able to comply with study requirement.
3. Female or male, aged 18 years or above.
4. The patient must at the enrolment visit be identified for the first time as partial responder to PPI treatment as defined by the following criteria:
    a) At least 6 month history of GERD symptoms (need not be consecutive)
    b) Continuously treated with unchanged optimized PPI treatment for any GERD indication during the last 4 weeks (an optimized PPI treatment is a treatment, which according to the investigators 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 continuously treated with a PPI during the last 8 weeks before enrolment (optimized PPI treatment during the last 4 weeks before enrolment).
5. To be eligible for enrolment, the patients must have reported, in the RDQ-RI screening instrument using 7 days recall, a minimum of three days with at least one of the two following symptoms with at least moderate severity:
    - a burning feeling behind the breastbone
    - an unpleasant movement of material upwards from the stomach.

Exclusion Criteria:

1. Patients that have not experienced any GERD symptoms improvement at all during PPI treatment.
2. Prior surgery of the upper GI tract (open, endoscopic and laparoscopic surgery on the esophagus, the stomach and the duodenum with the exception of over sewing or endoscopic treatment of an bleeding ulcer)

3. Any other condition which in the opinion of the investigator would render the patient unsuitable for inclusion in the study.
4. Involvement in the planning or conduct of the study.
5. Previous enrolment in the present study.
6. Involvement in any other observational or clinical study at the time of this study.

6 SAMPLE SIZE

The target enrollment sample size for this study is 275 patients with GERD. An attrition rate of approximately 30% over the course of the twelve-month data collection period is expected as some patients will not complete and return the follow-up patient surveys, yielding a final sample size of ~200 patients for analysis.

Due to the descriptive objectives of the study, there are no hypotheses to test with statistical methods to predetermine a required sample size. Calculations based on a database study in the relevant patient group indicate that the sample size will result in satisfactory precision in estimates of individual items of resource utilization, symptom load, impact of symptoms on daily life and effect on work productivity.[17] Based on previous similar studies in other but related patient groups the sample size is also deemed to be sufficient to satisfactorily describe common treatment pathways.

7 STUDY PROCEDURES

7.1 Site Recruitment

Potential investigators will be identified from a global French database provided by Rosenwald and compiling more than 160 000 physician references. A representative sample of 500 physicians including both general practitioners (family doctors and internists) and specialists, i.e. gastroenterologists, will be extracted and invited to participate in this study. The assumed ratio between specialist and general practitioner is 1:1. A mass mailing will be sent out to gauge investigator's interest and to evaluate their ability to successfully participate.

All interested sites, sorted by region, will be assigned a random number and will then be sorted by ascending order. The first 50 sites will be selected to participate. In case of any change in site's willingness to participate the site number 51 will be contacted to supplement the list and then 52, 53 subsequently.

7.2 Site Training

The study physicians and designated staff will be responsible for recruiting subjects, obtaining informed consent, and collecting baseline subject information. Study physicians and designated staff will be required to complete study training prior to recruitment of study subjects. Physicians and designated staff will receive training via participation in one of a series of scheduled web-ex training presentations. Training provides step-by-step instructions on how to recruit patients for the study, obtain informed consent, complete the CRF, report medical events, and retain study documents.

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7.3 Subject Recruitment

Subjects will be recruited in community practice settings by approximately 50 study physicians in France. The target recruitment goal for each physician is 5 to 6 patients with GERD newly identified as partial responders with an upper limit of 14 per physician. Subjects will be enrolled during a normally scheduled office visit.

Enrollment will be closed once the target enrollment goal of 275 patients has been reached. Study physicians will be notified by telephone and fax memo that recruitment is closed.

7.4 Enrollment Visit: CRF

The study physicians will identify eligible patients at regularly scheduled office visits. Upon determining that the patient has at least 6 month history of GERD and has been identified as a first time partial responder to optimized PPI treatment, the study physician and/or designated staff will attempt to recruit the patient for the study. If a patient indicates that he or she is interested in participating, the physician will advise the patient of the nature of the study, study requirements, and study benefits using a study recruitment packet. The recruitment packet will include a study description, copy of the informed consent form, and a copy of the baseline patient survey.

The physician will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and will ensure that the subjects are notified that they are free to discontinue from the study at any time. This will also ensure that the subject is given the opportunity to ask questions and allowed time to consider the information provided.

The study physician will obtain informed consent from the patient and have the patient sign two copies of the informed consent form (ICF), one set of copies will be given to the patient to keep

and one set will be filed with the study materials for that patient. Signed and dated informed consent must be available before any other study procedures are conducted. Each patient will have a unique identifier assigned at the enrollment visit that will be used for all electronic and hard copy documents. Patients will officially be recruited in the study once they sign the informed consent form.

In order to finalize the screening process, the physician will confirm that the patient meets all study criteria as outlined in the CRF. Once this has been confirmed, the patient will, as a second step, complete the RDQ-RI. To be eligible for enrolment, the patients must have reported in the RDQ-RI screening instrument, using 7 days recall, a minimum of 3 days with at least one of the two following symptoms with at least moderate severity:

- a burning feeling behind the breastbone;
- an unpleasant movement of material upwards from the stomach.

The study physicians will also complete the visit 1 of the CRF for each subject to document enrollment into the study.

All subjects for whom a signed informed consent form and a completed baseline CRF, proving eligibility of the patient, are submitted will be considered enrolled in the study. Baseline CRF pages will also be collected for patients who fail study eligibility. The baseline RDQ-RI won't be collected for patient failing to one or more inclusion criteria from the baseline CRF. However, the baseline RDQ-RI will be collected for all the patients meeting all other baseline entry criteria, whatever there eligibility on this specific instrument (RDQ-RI).

7.5 Enrollment Visit: Patient Survey

At the time of the enrollment visit, study physicians and/or designated staff will provide to each subject a paper patient survey.

Sites will provide a private place, where subjects are not distracted and can concentrate on the completion of the questionnaires. Subjects will be asked to complete the general Health-related Quality of Life questionnaires first, followed by the disease specific questionnaires. After completion of the survey, subjects will be asked to return the completed documents to site staff in a sealed envelope for mailing back to i3. The package that will be mailed back to i3 will also contain the baseline RDQ-RI.

7.6 CRF: Resource utilization

The study physician will complete a hard copy CRF documenting the patient's medical resource utilization related to GERD such as office visits, prescriptions, hospitalizations etc at month 6 and 12 following study entry. Data regarding over the counter medication and visit to other

physicians will be collected from the patient directly via the patient survey document at month 3, 6, 9 and 12 from study entry.

7.7 Log of new GERD patients

A log of all newly diagnosed patients with GERD seen in the physician's office will be maintained during the duration of patient enrollment. This paper-based log will contain the following data fields to allow for the estimate of a ratio of all newly diagnosed patients with GERD and first time partial responders:

- Patient year of birth
- Patient gender
- Date of first GERD diagnosis / Date seen in Practice

This log will be returned to i3 at the end of enrollment period. A copy of the log will be kept on site.

7.8 Follow-Up Patient Mail Surveys

Quarterly follow-up patient surveys will be mailed to patients by the physician. In addition to the same set of self-administered questionnaires as completed during the initial visit, the package will also include an additional one or two pages dedicated to resource utilization data for over the counter medication and visits to other physicians.

Patients will return the completed survey by mail in a postage-paid return envelope to the CRO in charge of the data collection (i3).

To limit the number of non-responders to quarterly follow-up surveys, a reminder call will be placed to the study physician two weeks before the scheduled date. Upon the sites' confirmation, a second package will be sent to the sites for non-responders two weeks after the initial mailing, and will contain the same contents as the initial packet. Patients may be called to remind them to complete the surveys.

7.9 Study Assessments

Data will be collected using a case report form, a patient baseline survey, and four follow-up patient surveys at 3, 6, 9 and 12 months. A summary of each assessment appears in the sections below.

Schedule of Completion	Total Questions	V1	3 months	6 months	9 months	12 months
Physician CRF						
Eligibility and demographics, history, comorbidities	20	X				
Physician CRF / Patient Survey:						
Resource Utilization Hospital visits, physician's office visits, prescriptions	~10	X		X		X
Patient Survey:						
Resource Utilization						
Over the counter medication, other physicians			X	X	X	X
Anxiety & Depression						
Hospital Anxiety and Depression Scale (HADS)	14	X				X
Symptom Frequency and Severity						
Reflux Disease Questionnaire (RDQ-RI)	26	X	X	X	X	X
GERDQ	6	X		X		X
Quality of Life						
Quality of Life in Reflux and Dyspepsia (QOLRAD-RI)	25	X		X		X
EQ-5D	6	X		X		X
Short Form 36 (SF-36)	36	X		X		X
Work Productivity						
Work Productivity and Activity Impairment for Patients with Gastroesophageal Reflux Disease (WPAI-GERD)	6	X	X	X	X	X

7.9.1 Case Report Form (CRF)

The CRF will collect the following data:

1) Enrollment visit

- Patient characteristics:
    - gender
    - year of birth
    - height and weight
    - waist circumference
    - highest level of education
- Clinical information:
    - GERD treatment and history
- Concurrent medical conditions (e.g., hypertension, lipid metabolism disorders, heart disease, upper GI disorders) and medications;
- Type and dosage of PPI, duration of treatment

2) During the study

Additionally, the study physician will complete a CRF at month 6 and month 12 during the study using information from the patient's medical records to collect the following information:

- diagnostic procedures
- endoscopic procedures (e.g. endoscopy with or without biopsy, dilation of stricture),
- presence of Barrett's epithelium
- hospitalizations, emergency room, and office visits due to GERD
- specialist referrals due to GERD
- prescriptions for GERD

7.9.2 Patient Baseline and Follow-Up Surveys

The patient survey will include the following patient reported outcomes questionnaires:

Symptom Frequency and Severity

- The Reflux Disease Questionnaire (RDQ-RI) is a 26-item, self-administered questionnaire designed to assess the frequency and severity of heartburn, acid regurgitation and epigastric pain over the previous week[19]. A GERD dimension can be obtained by combining the heartburn and regurgitation dimensions, while the epigastric pain dimension is also known as the dyspepsia dimension.

Symptom frequency and severity are scored on a 6-point Likert scale, with higher scores indicating more frequent or severe symptoms.

- The GERDQ is a 6-item questionnaire that measures symptoms in the upper gastrointestinal tract.

Quality of Life

- The Quality of Life in Reflux and Dyspepsia – Reflux Inhibition (QOLRAD-RI) questionnaire is a disease-specific quality of life instrument comprising 25 items that ask subjects about the effect of upper gastrointestinal symptoms on five dimensions: emotional well-being, sleep, vitality, eating/drinking and physical/social functioning[20]. Subjects report the frequency of these effects 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), with low scores indicating a severe impairment of daily functioning.

- The SF-36 is a 36-item general quality of life instrument that measures physical functioning, bodily pain, and role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, general health problems, and perceived change in health. It yields an eight-scale profile of functional health and well-being scores as physical and mental health summary measures and a preference-based health utility index.[21] Item response categories range from dichotomous to six levels and are scored so that a higher score indicates a more favorable health state.

- The EQ-5D is a health-outcome measure that provides a descriptive profile and index value for health status.[22] Five questions comprise dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) across three levels (no problems, some/moderate problems, and extreme problems), in addition to one measure of health status on a vertical graduated (0-100) visual analog scale.

Anxiety and Depression

- The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-assessment designed to detect states of anxiety and depression among patients in an outpatient clinic setting.[23] Each item is answered by the patient on a four point (0–3) response category. The HADS yields an anxiety score and a depression score.

Work Productivity

- The Work Productivity and Activity Impairment for Patients with Gastroesophageal Reflux Disease (WPAI-GERD) questionnaire is a six question instrument that measures work productivity and activity impairment instrument over the past seven days due to GERD. [24] It yields four types of scores; absenteeism (work time missed), presenteeism (impairment at work / reduced on-the-job effectiveness), work productivity loss (overall work impairment / absenteeism plus presenteeism) and activity impairment. WPAI outcomes are

expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Patient resource utilization

A patient resource utilization instrument investigating about any over the counter medication taken by the patient during the 12 months during the study, as well as visits to other physicians will be provided to the patient together with the survey at month 3, 6, 9 and 12. A memory aid will allow the patient to track their medication between the survey dates.

7.10 Study Site Monitoring

No on-site monitoring will be conducted for this study. Study sites will be contacted by i3 staff out of the Study Management Center (SMC) at regular intervals during the course of the study to remind them to enter resource utilization data into the CRF. These contacts will include the pre-study qualification, initiation, interim monitoring, and close-out requirements. In addition, sites will be called every 3 months after enrollment visit of a patient to remind them to send out the survey package to the patient.

Study monitoring is conducted remotely via telephone contact. Sites will be asked to send in their CRFs on a regular basis to allow for early identification of potential issues.

Sites will be informed via phone of proper close-out activities after all data has been captured appropriately and no data issues are open in both studies. Final documents will be collected as needed.

8 DATA MANAGEMENT

i3 data management activities will comply with all applicable regulatory requirements and i3 established practices for collection and validation of data and preparation of a reliable database for statistical analysis. The project specific procedures will encompass all of the data management activities associated with the implementation and completion of the study observational plan. A formal data management plan will be prepared for the study. The data management plan will include security and access, data flow, data management, data handling, quality management, and documentation.

8.1 Case Report Forms

Physicians will complete the paper enrolment CRF at the time of the enrollment visit. At month 6 and month 12 the physician will additionally complete a paper CRF for collection of resource utilization data.

Physicians will provide a copy of the CRF and a copy of the informed consent form to i3. The completed CRFs are AZ Property and i3 Innovus will not disclose them to third parties, except for authorized representatives of AZ or appropriate regulatory authorities, without written permission from AZ. AZ will not receive Protected Health Information (PHI) contained in these CRFs.

The study physician will be responsible for completing, reviewing and approving the portion of the case report form relating to the enrollment visit and follow-up contacts.

8.2 Record Retention

To enable evaluations and/or audits by regulatory authorities or AZ, the study physician will be required to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, medical event reporting forms, and source documents for fifteen years after consenting and enrolling the patient.

9 ADVERSE EVENT

The Investigator should report potential adverse drug reactions as post marketing spontaneous reports to authorities/manufacturer of suspect drug(s) according to local procedures.

10 STATISTICAL ANALYSIS

10.1 Introduction

This section outlines the statistical methods that will be used for this study. A formal statistical analysis plan will be developed based on discussions with AZ. The list of tables to be produced will be part of this analysis plan. All analyses will be conducted using SAS version 9.1 for Windows.

10.2 Study Population

Two study populations are considered: the “log population”, which consists of all GERD patients approached for this study and the “per protocol population”, which consists of all patients enrolled in the study, satisfying to inclusion and exclusion criteria specified in section 5.

The proportion of partial-responders to PPI and analysis of screening failure will be conducted over the log population and the analyses of symptoms, patients reported outcomes, healthcare

resource use, productivity loss and associated costs will be performed on the per protocol population.

10.3 Descriptive Analysis

First, frequency tables reporting the characteristics of the log population, proportion of partial-responders to PPI and reason for exclusion will be prepared.

A descriptive analysis will first be undertaken. For continuous endpoints the following will be reported:

- mean
- median
- standard deviation
- 95% confidence intervals for the mean
- minimum
- maximum
- first and third quartiles.

The distribution plot of the variables will also be presented. For categorical variables, we will report frequency tables and histograms.

The following analysis will be reported by physician type (General practitioner, gastroenterologist) and overall.

- Descriptive statistics will be provided for patients' characteristics (age, gender, height, weight, BMI, smoking status).
- Medical history at study entry will be described using retrospective data collected from the physician. This will include the frequency of co-morbidities in partial responders to PPI (proportion of patients having each type of co-morbidities), time since diagnosis of GERD and treatment history of GERD. The treatment history will be described via the proportion of patients having used each type of healthcare resource use and the mean level of resource use by type (diagnostic test by type, surgery, referral to a specialist, prescribed medication by type, dose and frequency).
- The medical treatment pathways will be further described by reporting the proportion of patients receiving each medication as first, second and third treatment and by reporting the frequency of each possible strategy (defined via the sequence of medications prescribed to the patient).

- Symptom frequency and severity scores (based on RDQ-RI and GERDQ) will be reported by visit. Graphs providing the mean score value and 95% confidence interval over time (at visit 1, then 3, 6, 9, 12 months) will be prepared.
- For each quality of life and patient reported outcomes questionnaires (SF-36, QOLRAD - RI, EQ-5D), item, domain and total scores will be estimated according to the scoring instructions from each questionnaire. Each type of score (item, domain and total) will be reported by visit using tables and graphs indicating the mean value and 95% confidence interval over time.
- Work productivity loss will be described via the proportion of patients having experienced work absenteeism, presenteism (presence at work but with a reduced productivity), the mean number of workdays lost and the overall productivity loss because of GERD. These statistics will be reported by visit.
- Resource use (proportion of patients prescribed each type of healthcare resource and mean level of resource use) will be reported by visit. Proportion of patients receiving prescribed medications and OTC medications will be reported by type of medication. The mean number of treatment days will also be reported.

10.4 Calculation of Direct Costs: Medical Resource Utilization

Using physician-reported resource utilization data and OTC medications collected from the patients, unit cost for individual services will be derived for the purpose of estimating costs. Following database lock, a unique list of the health care resources reported will be obtained and unit costs for each resource will be identified from standard costing sources. Standard cost sources will include national administrative databases (e.g., hospitalization, ER visit) and patient surveys for outpatient procedures. Unit costs of medications will be obtained from the Vidal. These unit costs will be applied to the resource utilization reported by the patients and used to calculate overall costs of healthcare. Costs will be computed from the third party payer perspective.

The mean cost of healthcare will be reported by visit (at study entry, 6 months and 12 months) and type of healthcare resource use.

The mean cost of healthcare resource use will also be reported by physician type (GP vs specialist), patients' characteristics (age class, gender, BMI class) and frequency and severity of symptoms. The summary statistics will be reported over time and by group in the form of tables and graphs.

10.5 Calculation of Indirect Costs: Productivity

Days of work missed due to GERD and obtained from the WPAI-GERD will be converted into monetary amounts utilizing earnings data from the national statistics (INSEE).

The mean cost of productivity loss will be reported by visit (at study entry, 6 months and 12 months) and type of productivity loss (absenteeism, presenteeism, overall).

The mean cost of productivity loss will also be reported by physician type (GP vs specialist), patients' characteristics (age class, gender, BMI class) and frequency and severity of symptoms.

10.6 Multiple regression

To investigate the link between symptom (frequency and severity) and QOL we propose to conduct a number of analyses consisting of correlation analysis, graphical analysis and generalised linear modeling. GLM are selected to account for underlying distribution of endpoint of interest (non-normal). We would model QOL score as a function of patients' characteristics, symptoms, adverse effects and medical history, to quantify the impact of each factor on the QOL impairment. Similar types of analyses would be performed for resource use, productivity losses and costs.

In addition we will develop longitudinal models to understand the evolution of the study endpoints over time to quantify the consequences of reducing the symptom frequency and/or severity in terms of costs, quality of life and utility values. We would use generalized estimating equation modeling to model the study endpoint dynamically and account for the between-patient heterogeneity. Generalised Estimating Equation models would be used here to estimate the heterogeneity between-patients vs within patient and to understand the impact of change in symptoms (reduction of frequency, severity) on study endpoints. These analyses would be performed for HRQOL, utility values, productivity loss, healthcare resource use.

Bivariate analyses will be conducted to assess whether each factor of interest (patients' characteristics and symptoms frequency and severity) significantly affects quality of life, resource use, productivity loss and associated costs. The heterogeneity between sites and between patients will be reported via the analysis of intraclass coefficients.

The results of these preliminary analyses will be used to develop generalized linear mixed model, accounting for the underlying distribution of the modeled endpoints and the clustering of the data (patient's repeated measures nested within sites).

10.7 Cost of Illness Analysis

The first step of this analysis will consist of estimating the size of the target population. A literature review will be undertaken to obtain the incidence and prevalence of GERD in France and the proportion of patients treated in primary care and secondary care. The proportion of

patients with GERD with incomplete response to PPI will be calculated from the sites' log. The proportion of partial responders will be reported by site, physician type and overall, together with 95% confidence intervals. The size of the target population (partial responders to PPI) in France will then be derived.

Based on the information obtained from the cost of healthcare resources collected alongside this study, we will be able to estimate the cost of partial response to PPI within the year of partial response diagnosis. Some assumptions will be made on the basis of the literature and clinical experts' opinion to estimate the mean cost of treatment over subsequent years. The cost of partial response to PPI will be reported overall and by type of resource (GP visits, specialist visits, diagnostic tests, hospitalization, prescribed medications and OTC medications) for France.

11 ETHICAL & REGULATORY CONSIDERATION

11.1 Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS)

Unlike an interventional clinical study, this observational non interventional study does not require a submission to Health authorities and Ethics Committees. However, the study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with applicable parts of ICH/Good Clinical Practice.

In accordance to applicable law, this protocol will be submitted for evaluation to CCTIRS for opinion and recommendation on study methodology and review of the study's compliance with local laws for the protection of personal data.

11.2 Commission Nationale Informatique et Liberté (CNIL)

Following the process of CCTIRS and in accordance with the data protection law the protocol as well as patient information and the consent form are submitted to the CNIL for approval.
The informed consent form will integrate the reference to the specific law and inform the patient on his rights regarding the personal data collected during the course of the study.

11.3 Conseil National de l'Ordre des Médecins (CNOM)

The physician will receive compensation for his participation in this trial. This compensation will be clearly detailed in a financial agreement that will form part of the site contract. The site

contract will be submitted to the CNOM for their opinion. In addition, the physician will be responsible to inform his local council about his participation in the trial and corresponding compensation.

11.4 Regulatory considerations

The study is designed to follow Good Epidemiology Practice (GEP Guidelines) and the applicable parts of the Good Clinical Practice standards as set forth in the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP Guidelines), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as identified below:

- 2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society
- 2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation
- 4.8 Informed Consent of Trial Subjects

In addition, the study will run in accordance with the applicable SOPs as outlined in detail in the project plan.

12 PRIVACY AND SECURITY

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to investigate the outcomes identified for this study and will be in compliance with applicable data privacy protection laws and regulations.

Explicit consent for the processing of personal data will be obtained from the participating patient before collection of data. Such consent will also address the transfer of the data to other entities, including the sponsor, doctors and healthcare professionals taking part in the study.

13 EARLY TERMINATION OF STUDY

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the Committee, or at the discretion of AZ.

If a study is prematurely terminated or discontinued, AZ or its contracted agents will promptly notify each study physician. After notification, participating subjects will be contacted within ten (10) days. As directed by AZ, all completed study materials must be collected and all CRFs

completed to the greatest extent possible. Any unused study materials will be destroyed by investigators.

14 ADMINISTRATIVE AND LEGAL OBLIGATIONS

14.1 Protocol amendments

Protocol amendments must be reviewed and approved by AZ. Agreement from i3 must be obtained for all protocol amendments and amendments to the ICF. The CCTIRS and CNIL must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the study. i3 will send a copy of the written approval from the committees to AZ.

14.2 Study termination

AZ reserves the right to terminate the study. i3 will notify each sites' study coordinator of the termination of the study.

If a study is prematurely terminated or discontinued, AZ or its contracted agents will promptly notify each study physician. After notification, participating subjects will be contacted by the physician. As directed by AZ, all completed study materials must be collected and all CRFs completed to the greatest extent possible. Any unused study materials will be destroyed by investigators.

14.3 Study documentation and storage

Source documents are original documents, data, and records from which the subject's data are obtained. Case report form and other survey instrument entries may be considered source data if the CRF or other survey instrument is the site of the original recording (i.e., there is no other written or electronic record of data).

i3 will maintain a comprehensive and centralized filing system of all study related (essential) documentation per i3's Study Master File (SMF) SOP, suitable for inspection at any time by representatives from AZ.

Study-related documentation includes patient files containing completed CRFs, supporting copies of source documentation, regulatory files containing the protocol with all amendments, all ICFs, all survey instruments and all correspondence to and from the Committees and AZ.

14.4 Language

Case report forms will be completed in English and patient surveys must be completed in French. All written information and other material to be used by patients and site personnel must use vocabulary and language that are clearly understood and will be in French.

14.5 Publication policy

AstraZeneca is committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "*Each author should have participated sufficiently in the work to take public responsibility for the content"*.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet all three conditions.

AstraZeneca intends to publish the results of the study within 12 months of the end of the study.

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Appendix A. GERD Patient Log Form

Please record the following information for each new GERD patient seen in your office during the study. For each patient newly diagnosed with GERD, please indicate: 1) the date the patient was seen in your office, 2) the patient's year of birth, 3) the patient's gender.

	Date of diagnosis / date seen in practice	Patient Year of Birth	Gender

PROTOCOL SIGNATURE PAGE

Observational Protocol:

Partial Response to PPI-treatment: the Cost to Society and the Burden to the Patient

REMAIN - France

Version: 1.1

Final:

PROTOCOL SIGNATURE PAGE

Observational Protocol:

Partial Response to PPI-treatment: the Cost to Society and the Burden to the Patient

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