Health Economics/Outcomes Research Methodological Protocol

Drug Substance Nexium, LDA

Study Code D961FC00004

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

Sponsor:

AstraZeneca R&D Molndal
S-431 83 Molndal
Sweden

The following Amendment(s) and Administrative Changes have been made to this protocol:

Amendment Number	**Date of Amendment**	**Local Amendment Number**	**Date of local Amendment**

Administrative change Number.	**Date of Administrative Change**	**Local Administrative change Number**	**Date of local Administrative Change**

PROTOCOL SYNOPSIS

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

Investigator

To be named.

Study centre(s), and number of subjects planned

Approximately 2000 subjects will be recruited from up to 80 centers in 3 countries (USA, Canada and France) and will be completing a one-time survey. Four hundred twenty (420) of these subjects will be followed for three months, with up to a maximum of 20 of these subjects undergoing personal interviews.

Study period
Estimated date of first subject enrolled
Estimated date of last subject completed

Objectives

The broad objective of this exploratory, observational, study is to characterize upper GI (Gastrointestinal) symptoms in subjects with Cardiovascular (CV) risk or confirmed disease taking low-dose aspirin (LDA) for primary or secondary CV disease prevention. More specifically, the study will:

- Characterize the frequency and nature of the upper GI symptoms
- Observe and record upper GI symptoms and compliance with LDA, and other relevant medications.
- Document the subject's behaviour, subjective experience, and evaluation of their condition (e.g., sleep, GI events, doctor's visits, etc.)

Study design

This is an observational study design delivering up to 15 months of data of which 12 months are retrospective and 3 months prospective. It consists of three stages: a one-time, cross-sectional survey; a prospective, three month diary; and, a personal (cognitive) interview. All data will be captured from subjects in the context of their usual care for CV disease, or risk for CV disease as ascertained by their physician, as such there will be no study treatment or intervention.

Target subject population

Females and males 18 years and above who have been prescribed low-dose aspirin (LDA) within the past 12 months, 75-325 mg, o-d owing to cardiovascular (CV) risk factor(s) and or disease(s).

Outcome variables

Given the exploratory nature of the observational study a variety of outcome variables representing a number of domains will be measured. These will consist of demographics, medical and surgical history, with special attention to GI symptoms/diseases and concomitant medication. In addition, a variety of Patient Reported Outcomes (PRO) instruments will be utilized.

Patient Reported Outcomes (PROs)

PRO domains measured will include but not be limited to: GI symptoms, medication usage, medical history, healthcare utilization, daily activities, coping strategies, communication & relationship with their physician, sleep patterns and mood.

Health economics (not applicable)

Not applicable.

Statistical methods

A variety of statistical techniques appropriate for characterizing observational data and examining the study objectives will be applied. The complete analytic approach will be outlined in a separate Statistical Analysis Plan (SAP).

TABLE OF CONTENTS PAGE

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

LIST OF APPENDICES

LIST OF SUPPLEMENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
ASA	Acetylsalicylic acid
CRA	Clinical Research Associate
CRF	Case Report Form
CSP	Clinical Study Protocol
CV	Cardiovascular: referring generally to the cardiovascular system
EMA	Ecological Momentary Assessment: a method that measures real-time behaviours, subject's self-reports and perceptions so as to reduce bias from various cognitive confounds. Various modalities can be used to capture this information (e.g., paper, electronic etc.)
ePRO	Patient Reported Outcomes that are specifically collected via electronic devices
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
GCP	Good Clinical Practice
GI	Gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
HE	Health Economics: Evaluations assessing and comparing the cost and consequences of different treatment options.
HRQL	Health Related Quality of Life: Multidimensional, subjective patient-reported outcomes.
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
LDA	Low Dose Aspirin – referring to doses of 75-325 mg.
OR	Outcomes Research: The study of health related quality of life, health outcomes such as symptoms, sleep disturbances, physical functioning and subject or treatment satisfaction i.e., Patient-Reported Outcomes.
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective.

Abbreviation or special term	Explanation
Parameter	A quantity (usually unknown) that characterizes the distribution of a variable in a population of subjects.
PDA	Personal Digital Assistant a small handheld electronic device that is used to capture and store information.
Principal Investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a Principal Investigator.
PRO	Patient-Reported Outcomes: Umbrella term categorising various types of subjective reported outcomes such as health-related quality of life, treatment satisfaction, subjective health status and subjective symptoms directly from the subject.
RDQ	Reflux Disease Questionnaire
SAP	Statistical Analysis Plan
SitePro	A PDA device that will be used to collect data electronically in the physicians office.
TS	Treatment Satisfaction: A comparison between perceived quality (good-poor) of a given treatment and the subject's initial expectations.
UGI	Upper Gastrointestinal
XQS	Extraesophageal Questionnaire Scores

1. INTRODUCTION

1.1 Background

For at least 2 decades low-dose acetylsalicylic acid (LDA) has been used for the prevention of thromboembolic events. The dose range of LDA is 75 to 325 mg daily. The individual doses for different indications vary between countries. The antithrombotic effect of LDA seems to be similar within the dose range of 75 to 325 mg daily (Patrono C et al 2005).

Continuous low-dose ASA treatment is accompanied by a variety of undesirable AEs. These include upper gastrointestinal (GI) symptoms such as dyspeptic symptoms, abdominal pain and/or heartburn (Silagy CA et al 1993, Laheij RFJ et al 2003), peptic ulcers which might be followed by serious ulcer complications such as bleeding, gastric or duodenal perforation and obstruction (Lanas A et al 2006, Yeomans ND et al 2005, García Rodrígues LA and Hernández-Díaz S 2004, CAPRIE Steering Committee 1996, Weil J et al 1995). Even taking ASA in doses as low as 75 mg daily significantly increases the risk of having symptomatic peptic ulcer as well as the risk of having upper GI bleeding compared with not taking aspirin (García Rodrígues LA and Hernández-Díaz S 2004, Weil J et al 1995, Laine L 2006).

While the risk, nature, and development of ulcer and ulcer complications associated with LDA treatment is well documented, less is known about upper GI symptoms. The nature, occurrence rate, and impact of upper GI symptoms associated with LDA treatment, as well these symptoms' potential influence on compliance with LDA treatment, use of acid inhibitory drugs and other medications is the focus of the current study.

To understand how symptoms develop and are experienced, it is best to ask the subjects themselves (i.e. a patient reported outcome, PRO). Further it is important to understand these symptoms in a non-interventional, naturalistic environment. As such any methodology used needs to be aimed at observing, rather than influencing, the symptoms of interest. Historically, cross-sectional PRO surveys and face-to-face interviews have been used to evaluate subjects symptoms and disease experience. While useful for understanding the subjects' global perspective on their condition, retrospective recall is known to be problematic for documentation of the subjects' day-to-day experience.

To overcome the limitation of retrospective recall, real-time methods have been developed. Specifically, Ecological momentary assessment (EMA) is a method for gathering reliable data on subject events and experiences as they are occurring in real-time (Stone A et al 2003, Stone & Shiffman 2007). EMA methods have been successfully applied to gain understanding of how emerging disease processes and subject behaviour interact. Capturing real-time data from subjects using EMA methods yields a rich data stream that is then subject to statistical techniques that extract trends and offer potential links between behaviour and disease process. In settings such as the current one, where the GI symptom emergence and experience is not well understood, EMA methods are indicated.

1.2 Rationale for this study

Observing and documenting upper GI symptoms from a subject perspective will yield a better understanding of the nature of the symptoms (e.g., frequency, character, and how they emerge), the significance and impact of symptoms (e.g., impact on health related quality of life, and role in LDA non-compliance), and potentially point to ways of avoiding symptoms when these are a barrier to optimal CV risk management.

2. STUDY OBJECTIVES

The broad objective of this exploratory, observational, study is to characterize upper GI symptoms in subjects with CV risk or confirmed disease taking LDA for primary or secondary cardiovascular disease prevention. More specifically, the study will:

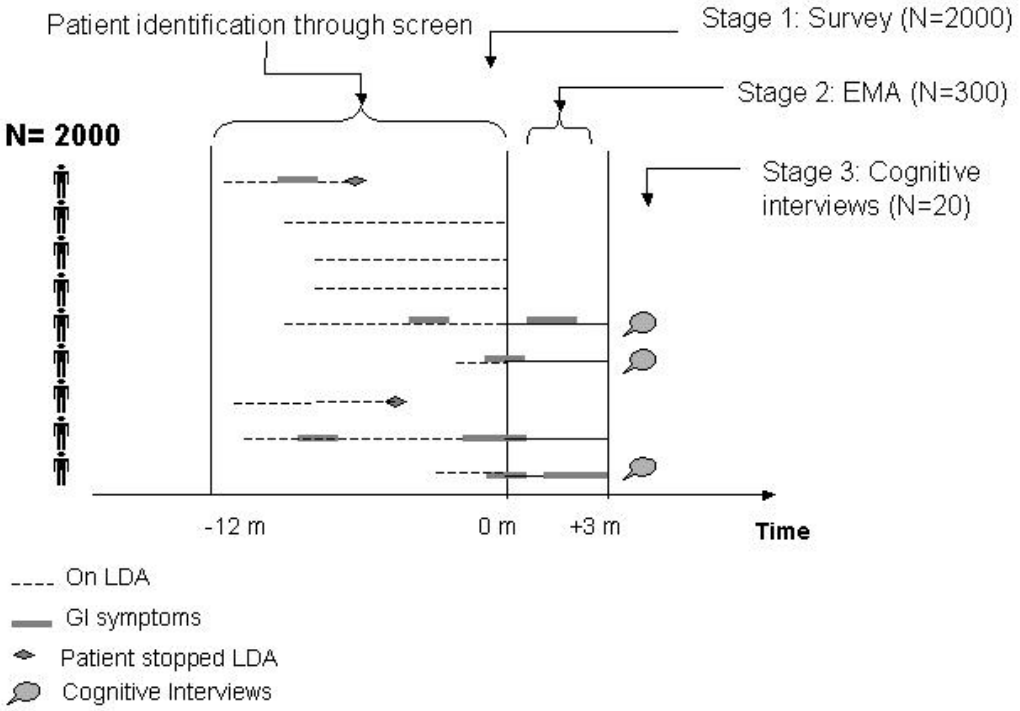
- Characterize the frequency and nature of the upper GI symptoms
- Observe and record upper GI symptoms and compliance with LDA, and other relevant medications.
- Document the subject's behaviour, subjective experience, and evaluation of their condition (e.g., sleep, GI events, doctor's visits, etc.).

3. STUDY PLAN AND PROCEDURES

3.1 Design and study flow synopsis

This is an observational study design delivering up to 15 months of data of which 12 months are retrospective and 3 months prospective. It consists of three stages: a one-time, cross-sectional survey; a prospective, three month diary; and, a personal (cognitive) interview. All data will be captured from subjects in the context of their usual care for CV disease or risk, that is, there will be no study treatment or intervention. Figure 1 is a graphical summary of the three stages.

Figure 1 Flow Chart



In the first stage of the study, approximately 2,000 subjects who have been prescribed LDA usage in the past 12 months, or those about to begin LDA, will complete a one-time in-office survey using an electronic personal digital assistant (PDA) device (termed SitePro). The survey will ask subjects about:

- Use of LDA (75-325 mg daily);
- subject's experience, if any, of UGI symptoms during the time they were using LDA;
- the impact of UGI symptoms on the subject's compliance with taking LDA and medications related to their CV disease or CV risk factors;
- background information about subject's emotional state and well being.

The specific domains that will be assessed, and the actual items of the survey are listed in Section 4.2.1, and Appendix C. Additional information such as medical history and concomitant medications will be captured by the investigator using a paper CRF.

A subset of the subjects of whom all complete the survey will be invited to participate in a three (3) month prospective diary period where real-time assessments will be administered using the ecological momentary assessment (EMA) approach. Four hundred, twenty (420) subjects stratified into three groups varying on length of time using LDA will be asked to use

an electronic PRO device (ePRO) to record information about their experience with LDA for the period of 3 months. The ePRO device will prompt (via an audible alarm) the subject three (3) times each day and administer questions regarding the subject's experience with LDA. In particular, the ePRO device will ask subjects about UGI symptoms, medication use, and about their daily activities and mood. The areas of assessment are listed in Section 4.2.1 (Table 2), and the specific questions are listed in Appendix D. The goal is to obtain EMA data from 350 subjects in the three groups: 200 Naïve LDA users (240 enrolled) who begin LDA use at the time of the study; 100 Short-term LDA users (120 enrolled); and, 50 Long-term LDA users (60 enrolled). A detailed description of the inclusion/exclusion criteria for each EMA group can be found in Section 3.3.3.

Finally, a sample of up to 20 subjects from the three EMA groups will be interviewed (see Section 3.3.4) to further debrief their experience with LDA and upper GI symptoms. This 1 hour cognitive interview will include the following areas:

- the subject's experience with upper GI symptoms;
- the subject's use of and compliance with LDA and other CV related medication;
- the subject's perceived impact of upper GI symptoms on their ability to continue with medication;
- the broader impact of these symptoms on their life.

The subjects will be selected following review of Diary/EMA data, and investigators will be asked to invite selected subjects to participate in these interviews.

3.2 Rationale for study design

In order to gain a comprehensive view of upper GI symptoms in subjects with CV risk or disease on LDA, survey, interview, and EMA data will be captured from subjects. Such data will capture the natural history of the emergence and course of UGI symptoms in subjects taking LDA. Further, the impact of these symptoms on subject behaviour will also be recorded in a naturalistic, non-intervention setting. In sum, the design will allow the naturalistic study of the phenomena and will yield data that addresses the objectives of the study.

3.3 Selection of study population

3.3.1 Study selection record

Subjects will be identified through their primary care, cardiologist or practice group and asked to participate in the study. The investigative site will screen eligible subjects and inform them of the opportunity to participate in the study. Subjects 18 years of age and older, diagnosed as at risk or confirmed with CV disease, and who have been prescribed LDA in the past 12 months or are about to commence LDA will be asked to participate. Subjects interested and

qualified to participate will complete an informed consent and have questions answered by the investigator or site staff. Subjects meeting the inclusion/exclusion criteria for the survey will be asked to complete the survey on an SitePro device. Those completing the survey, and identified by the survey SitePro tool as potential EMA candidates, will be further reviewed for inclusion/exclusion into the Diary/EMA stage of the study. Subjects meeting the EMA inclusion/exclusion will be invited to participate in the EMA portion of the study. The specific inclusion/exclusion for each of these stages is delineated below.

3.3.2 Survey inclusion/exclusion criteria

3.3.2.1 Inclusion criteria

- Provision of signed written inform consent.
- Female or male aged 18 years and over.
- Physician prescribed or recommended daily intake of LDA (75-325 mg daily) for cardiovascular disease prevention within the past 12 months, including the day of entry into the study.
- Established cardiovascular disease, such as (but not restricted to) CAD (Coronary Artery Disease), previous TIA (Transient Ischemic Attack) or ischemic stroke (secondary prevention), or subjects with known risk factors for cardiovascular disease without having experienced cardiovascular events previously (primary prevention).
- In the judgement of the investigator, the subject is able to carry out the procedures required by the CSP.

3.3.2.2 Exclusion criteria

- Need for concomitant treatment with a non-ASA NSAID including a cyclooxygenase-2 (COX-2) selective NSAID. Occasional use of up to 1 day/week is allowed.
- Involvement in planning and conduct the study.
- Inability to read and understand how to complete electronic questionnaires.
- Hospitalised.
- Subjects with a history of alcohol or drug abuse that in the opinion of the investigator would contraindicate their participation in the study.

3.3.3 Diary/EMA inclusion/exclusion criteria

3.3.3.1 Inclusion criteria

In addition to the inclusion/exclusion for the survey, subjects will meet the following specific criteria for each of the EMA groups:

Group 1: "LDA Naïve Users". These subjects will have been prescribed and will use LDA on the day they are invited to participate in the study. Subjects will not have reported any UGI symptoms in the past 14 days. One half (1/2) of the subjects in this group should have a history of having used a medication or remedy for upper GI symptoms in the past 12 months.

Group 2: "Short-term LDA Users". These subjects will have been prescribed and having used LDA within a 14-day period of Visit 1, have reported one or more UGI symptoms during that 14-day period, and reported not having used any H2 blocker or PPI during the same period.

Group 3: "Long-term LDA Users". These subjects will have been prescribed and having used LDA for at least 12 weeks and up to 12 months prior to Visit 1 or screening, have reported one or more UGI symptoms during the past 14-day period and having been prescribed or recommended a medication for acid suppression (H2 blockers or PPIs).

Subjects will be allocated to the groups according to their responses on the SitePro survey (see above), and the application of the inclusion/exclusion criteria by the investigative site.

3.3.3.2 Exclusion criteria

- Concomitant treatment with a non-ASA NSAID including a cyclooxygenase-2 (COX-2) selective NSAID. Occasional use of up to 1 day/week is allowed.
- Hospitalised at the time of the survey or EMA entry.
- Planned hospitalisation during the EMA data collection period (3 months).
- Inability to complete the diary daily.

3.3.4 Inclusion/Exclusion criteria – Cognitive interview

The inclusion of subjects into the cognitive interviewing will be based upon a review of the Diary/EMA data. The exact criteria will be determined in conjunction with AstraZeneca and depend upon the patterns of subject response emerging in the EMA reports during the study.

3.3.5 Restrictions

Not Applicable.

3.3.6 Discontinuation of subjects from assessment

3.3.6.1 Criteria for discontinuation

Subjects may be discontinued from study at any time. Specific reasons for discontinuing a subject from this study include:

1. Voluntary discontinuation by the subject who is free at any time to discontinue his/her participation in the study without prejudice to further treatment;

2. Severe non-compliance to the CSP as judged by the investigator and/or AstraZeneca;

3. Incorrect enrolment; i.e., enrolment in violation of the inclusion/exclusion criteria:

4. Subjects who are not completing at least 80% of their evening reports, indicating non-compliance with the diary recording requirements of the CSP:

5. If a physician recommends that the subject discontinue use of LDA, the subject will be discontinued from the study:

6. Intake of concomitant medication prohibited by the CSP.

3.3.6.2 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation. Any ePRO instruments should be returned by these subjects.

3.3.7 Method of assigning subjects to study groups

Informed consent will be obtained before enrolment in the study and the subject identified with an enrolment number. Given the observational nature of the study, randomization into a treatment group will not occur. Placement into one of three EMA groups will take place using the SitePro device as described above (Section 3.3.3.1).

If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

3.4 Study plan and visit procedures

The study plan outlining visits and procedures is shown below.

Table 1 Study plan

Visit Nos. Assessments	Visit 1 Day 1	Visit 2 Day 45 +/-7 days	Visit 3 Day 90 +/-7 days	Cognitive Interview Visit 3 +45 days
Informed consent	X			
Demographics	X			
Medical/surgical history	X			
Concomitant medication	X			
Inclusion/exclusion criteria	X			
SitePro Survey	X			
Training on ePRO Diary device	X			
Review subject's performance with ePRO device		X	X	
Conduct cognitive interview				X

3.4.1 Visit Procedures

3.4.1.1 Visit 1

Subjects visiting their physician for a "usual care" visit will be asked if they would like to participate in the study. They will be informed of the nature of the study and the requirements and that each component of the study will occur in succession and that they may not qualify for all stages.

If subjects choose to participate, they will be asked to read and sign an informed consent. Basic demographic and medical information will be collected by the Investigator or a designee using a paper CRF. Subjects will then complete the survey utilizing an electronic SitePro device while still at the investigative site. Questions will include, but will not be limited to: upper GI symptoms, LDA use, medication taking behaviour and other information relevant to the objectives of the study. The specific domains that will be assessed, and the actual items of the survey are listed in Section 4.2.1, and Appendix C. Additional information will be captured by the investigator using a paper CRF.

Following completion of the survey, the SitePro device will apply a preset eligibility algorithm to a subject's data and determine eligibility for one of the 3 Diary/EMA groups. Once eligibility is confirmed following review by the investigative site staff, the subject will be invited to participate in the Diary/EMA phase of the study. Subjects who are not eligible will be thanked for their time and then discontinued from the study.

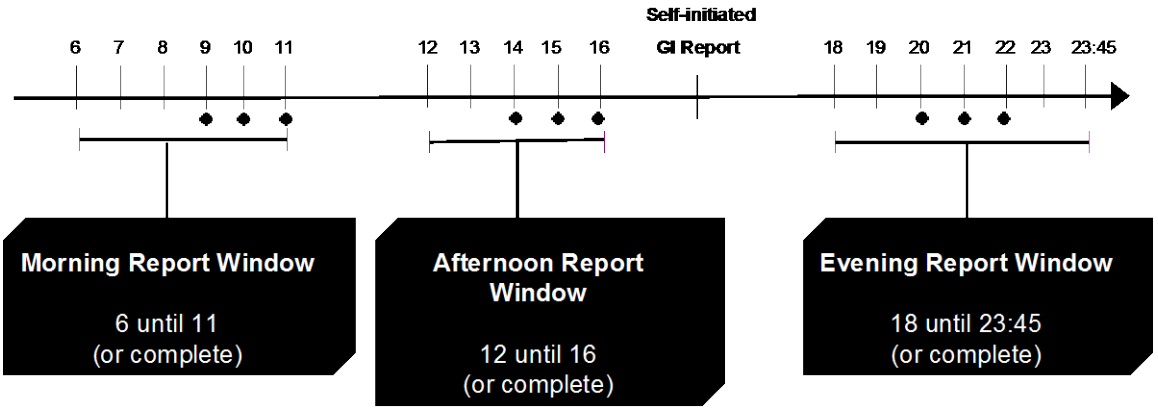
Subjects who agree to participate in the Diary/EMA phase will then be trained on the procedures and the use of the ePRO diary device by the investigative site staff. Training on

the ePRO will follow a standardized training program and include both printed materials and hands-on activities on the ePRO device itself.

Once trained, subjects will be sent into the field to capture data on a daily basis using the ePRO device. Each day the ePRO device will prompt (via an audible alarm) the subject three (3) times each day and administer questions regarding the subject's experience with LDA. In particular, the ePRO device will ask subjects about upper GI symptoms, medication use, and about their daily activities and mood. The ePRO-EMA diary-assessment is outlined in Section 4.2.2, specific questions are listed in Appendix D. Additionally, subjects can make entries into the ePRO device at any time about any discrete episode of UGI symptoms that they experience. Upon making an entry, the device will administer questions about the nature of the episode.

The structure of how the ePro diary device will prompt the subject over the course of a day is depicted below.

Figure 2 ePRO Device daily window schematic



After following these daily procedures, the subjects will put the ePRO device onto a charging device that also contains a modem to transfer data. Each night, the device will automatically (without subject intervention) utilize the modem to transfer the subject's data to a central data server. The investigative site staff will be expected to review subject compliance with EMA procedures utilizing web access to the data on the central server.

Between this and the next visit, the investigative site may be contacted by a Clinical Research Associate (CRA) if individual subjects are not compliant with the EMA procedures.

3.4.1.2 Visit 2

Approximately 45 days after Visit 1, subjects will return for a review of their compliance with the Diary/EMA procedures. During this visit, the investigative site staff will transfer data

from a subject's ePRO device to the central data server. A review of the subject compliance with the Diary/EMA procedures will then be performed utilizing a web access to the data. Subjects who are not complying with procedures will be given feedback, asked if they are experiencing specific problems, and then asked to comply with procedures for the remainder of the EMA period.

Subjects will be subject to the usual clinical care of the investigative site. No procedures beyond the compliance review are required.

Between this and the next visit, the investigative site may be contacted by a CRA if individual subjects are not compliant with the EMA procedures.

3.4.1.3 Visit 3

Approximately 45 days after Visit 2, subjects will return for their final Diary/EMA visit. During this visit, the investigative site staff will again transfer data from the subject's PRO device to the central data server. A review of subject compliance with the Diary/EMA procedures will then be performed utilizing a web access to the data. The subject's device will also be collected by the investigative staff.

Subjects will undergo the usual clinical care of the investigative site. No procedures beyond the compliance review and collection of the ePRO device are required, with the exception of those subjects selected for cognitive interviews.

3.4.1.4 Cognitive interview

During the period between Visit 2 and 3, subjects' data will be reviewed by the AstraZeneca study team. Up to a maximum of 20 subjects will be identified and invited to participate in a 1 hour interview with a trained interviewer. The subjects invited to participate in the interviews will be a sample of convenience. The interview may take place at Visit 3, or a separate visit may be scheduled for the sole purpose of the cognitive interview.

Only those subjects who can speak and understand English will be scheduled for an interview. The subject's permission will be sought to audio record the interview. Subjects who do not give permission for the audio taping will not be interviewed. The cognitive interview will include the following areas: the subject's experience with upper GI symptoms; the subject's use of and compliance with LDA and other CV related medication; the subject's perceived impact of upper GI symptoms on their ability to continue with medication, and the broader impact of these symptoms on their life.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Screening and demographic measurements

At Visit 1, demographic data, (e.g., date of birth, sex, race, and nicotine use) will be recorded. Medical and surgical history as well as GI and cardiovascular history will be obtained and recorded on a paper CRF. The investigator will use this and other information from the subject survey to perform eligibility checks to ensure that the subject is suitable for the study.

4.2 Measurement of outcome variables

The outcome measures in this study will include those from the subject survey and the EMA phase.

4.2.1 Cross–sectional survey (stage 1)

The following areas or domains will be assessed in the cross-sectional survey. The table below contains sample items or the name of an existing questionnaire. The full listing items for the survey, including all questionnaire items are shown in Appendix C.

Table 2 SitePro Survey Domains

Domain	Explanation
Background	Items about gender and LDA use will be entered to facilitate decision on EMA qualification and group.
UGI screening symptoms	Subjects will be asked about UGI symptoms for the past 14 days.
PPI and H2 blocker usage	Evaluates subject use of PPIs and H2 blockers for purposes of EMA qualification, and UGI treatment.
Interaction between UGI and LDA	Evaluates subjects' attribution about UGI symptoms and LDA.
UGI symptoms past 7 days or over past year	Debriefing of UGI symptoms over past 7 days where appropriate, or over past year if no symptoms in past 7 days.
Hospital Anxiety and Depression Scale (HADS)	A subject evaluation on anxiety and depression.
Morisky Medication Taking Behavior Scale	Patients behavior and attributions regarding taking CV medication (modified from original blood pressure medication).
SF-8 Health Survey	A brief general quality of life assessment.
Subjective Symptoms Questionnaire (SSA-P)	Assessment of typical side effects from CV medications, including UGI symptoms.

4.2.2 EMA assessments (stage 2)

The areas that will be assessed in the Diary/EMA phase utilizing the ePRO device are outlined below and listed in detail in Appendix D.

Table 3 ePRO-EMA Diary Variables by Daily Measurement Time

Time point Measurement	Morning AM	Afternoon PM	Evening ER	Self-initiated SI
Sleep	X			
Mood	X	X	X	X
Activities	X	X	X	X
Eating/food	X	X	X	X
GI symptoms	X*	X*	X*	X
GI coping strategies	X*	X*	X*	X
Medication usage	X	X	X	X
Healthcare Utilization			X	

* If subject reported elevated symptoms on a screening question, then they would receive all GI symptoms similar to debriefing of a SI episode.

5. DATA MANAGEMENT

Data entry will be performed at each center by authorized study personnel into the paper CRF. The investigator will ensure that the data has been entered into the CRF within 24 hours after a subject has completed a visit. Completed paper CRF's will be reconciled against source documentation or medical records and then retrieved at the monitoring visits by the monitor and returned to ICON. The CRF will be scanned into the ICON CRF scanning system (OptICON) and from there data entry will occur. Data will be entered into the Oracle Clinical database and if it is necessary to clarify data, a query will be issued to the site. The monitor will follow up with sites to ensure timely completion of queries.

Subjects completing the survey will be asked a series of questions on a hand held device (SitePro). This data will be automatically transferred to the Invivo Data database and will not be monitored by the monitor.

Subjects that are selected for the ePRO-EMA/Diary phase of the study will be instructed how to use and electronic diary (ePRO diary) for completion of daily questionnaires and surveys. The ePRO diary will be pre-programmed with various reminders to the subject to complete scheduled assessments. Data from the ePRO diary will be transmitted automatically on a daily basis for review and integration with the study database. The assigned monitor will review reports from the Invivo Data database at regular intervals to ensure subject compliance. In the event of serious non-compliance the monitor will contact the site to inform

the Investigator or designee of the issues and the Investigator or designee will follow up with the subject to resolve the issues.

The data management plan written by ICON Clinical Research describes the methods used to collect, check, transfer and process clinical data in the study. It also clarifies the roles and responsibilities of the different functions and personnel involved in the data management process.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Determination of sample size

Given the exploratory nature of the study, no formal sample size calculations will be undertaken. The sample size for the three study phases was chosen so as to obtain a reasonable representation of the population presenting to physicians who have CV disease or risk and are on LDA.

6.2 Statistical methods

A brief description of the statistical methods used to examine data from each stage of the study are described below. Given the dynamic nature and complexity of the data, specific analysis will be further outlined in a formal SAP to be completed before database lock. Furthermore, given the exploratory nature and lack of hypothesis testing, no specific hypothesis testing for group differences will be utilized.

6.2.1 Cross-sectional survey data

Analysis of the data from the survey will primarily be descriptive statistics (e.g., measures of central tendency, correlation matrices) of the demographic characteristics of the sample, frequency of upper GI symptoms, and the nature of those symptoms. In addition, medication usage (amount, type duration of use etc.) will be assessed in relation to demographic, PRO instrument and upper GI related variables.

6.2.2 ePRO-Diary/EMA data

Data for the EMA subjects sub-sample will be examined following analytic techniques typically used in natural history studies (Stone & Shiffman 2007, Shiffman et al 1997). In such studies the same number of observations per subject is not expected. Rather, in natural history studies trends are analyzed utilizing General Estimating Equations (GEE; Zeger SL et al 1988), which allow for varying numbers of observations and take into account the clustering of data within subjects; allowing for the most appropriate autocorrelation structure for this type of data. The variables that will be entered into the GEE models will vary depending upon the specific study objective under evaluation. In general, there will be a focus on those variables related to the onset of upper GI symptoms, and those associated with change in LDA usage.

6.2.3 Cognitive debriefing interview

Cognitive debriefing will be conducted by trained personnel. Data from the subject recordings will be transcribed to paper and analyzed using a number of qualitative techniques particular to this methodology. Specific analysis will be outlined in the SAP.

7. STUDY MANAGEMENT

7.1 Monitoring

Before a site is asked to participate in the study the ICON monitor will complete a Pre-Study visit to each site. During this visit the monitor will:

- Determine if the site has adequate facilities to complete the study.
- Discuss with the Investigator (and other personnel involved with the study) their responsibilities with regards to the CSP adherence and the responsibilities of the ICON monitor. This will further be described in the Clinical Study Agreement with the Investigator.
- Discuss the CSP and the requirement of study participants to use a hand held device to record data.
- Discuss the attendance at the Investigator meeting.

Prior to the initiation of the study, each site will participate in a training session (Investigator Meeting) to ensure that the physician understands all requirements of the CSP, and his/her regulatory responsibilities as a participating physician. No subjects may be enrolled until the site-specific approvals are received and site training is completed. A study representative will follow up with each study site on a regular basis to verify the accuracy and completeness of the data reported on the CRFs and diaries.

During the study a monitor from AstraZeneca or its delegate will have regular contact with study sites. During any on-site visits the monitor will:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the CSP, that data is being accurately recorded in the case report forms.
- Perform source data verification in a random selection of subjects (a comparison of the data in the CRFs with the subject's medical records at the practice, and other records relevant to the study). This will require direct access to all original records for each subject (e.g., clinic charts).

- Discuss subject non-compliance issues and how to avoid these issues with future subjects.

The CRA will also monitor subject compliance in completing the daily questionnaires the EMA phase. The CRA will review specific reports taken from the database in order to identify non-compliant subjects. The CRA will follow up with the sites in order to inform the Study Coordinator of issues with non-compliance. The Study Coordinator will be responsible for following up with the subject. The monitor will be available between visits if the Investigator(s) or other site staff need information and advice on the CSP or its procedures.

7.2 Audits and inspections

Authorised representatives of AstraZeneca, ICON, a regulatory authority, or an Ethics Committee may visit the centre to perform audits or inspections, including source data verification.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the observational protocol, the Declaration of Helsinki, ICH/GCP and any national and international regulations applicable to post-authorization surveillance studies.

The investigator should contact the AstraZeneca representative (ICON) immediately if contacted by a regulatory agency about an inspection at his or her center.

7.3 Training of staff

Prior to Initiation of a site the Investigator or sub-Investigator and designee will attend an Investigator Meeting for their region. During the Investigator meeting the attendees will be trained on the CSP, regulations and on the use of the various hand held devices that will be used during the study.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved. The Principal Investigator or Study Coordinator, under the Principal Investigator’s direction, will train additional staff and if necessary this training will be performed by ICON CRA's.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If it is necessary for the CSP to be amended, the amendment and/or a new version of the CSP (Amended Protocol) must be notified to or approved by each Ethics Committee, and if

applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be must be notified to or approved by each Ethics Committee according to local requirements.

If a CSP amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the CSP to each Principal Investigator(s), who in turn is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

The Principal Investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this CSP and the Clinical Study Agreement, the CSP shall prevail.

7.6 Study timetable and termination

Before a subject's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- Approval of the study by the appropriate Ethics Committee(s).
- Approval of the study, if applicable, by the local regulatory authorities.

As per the EU Directives for subjects recruited in France, notification of Competent Authorities will be done within 90 days of Last Subject Out for the study.

8. ETHICS

8.1 Ethics review

Given the observational nature of the study and that data collected will contain only information derived from medical records and subject self-reported outcomes, no untoward risk is expected.

The final CSP, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate. The

investigator must submit written approval to AstraZeneca before he or she can enrol any subject into the study.

The Principal Investigator(s) is responsible for informing the Ethics Committee of any amendment to the CSP in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit subjects for the study. The CSP must be re-approved by the Ethics Committee annually, as local regulations require.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

8.3 Informed consent

Subjects will be identified through their primary care, cardiologist or practice group and asked to participate in the study.

The Principal Investigator(s) at each centre 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. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. Subjects will be informed that they may be asked to participate in all three phases of the study (retrospective survey, EMA prospective assessment and the cognitive debriefing) and that in order to participate in the EMA and cognitive debriefing they will have to have completed the previous phase.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study, including the following:

- completion of rating scales or questionnaire
- GI assessments
- cognitive debriefing interviews

The Principal Investigator(s) must store the original, signed Informed Consent Form (for 15 years). A copy of the signed Informed Consent Form must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorise the collection, use and

disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by enrolment number, study code and initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

8.5 Dissemination of results

Results of the study cannot be disseminated either through reports, presentations at scientific conferences, publications or any other means with out the express written consent of AstraZeneca. AstraZeneca intends to publish the results of the study within 12 months of the end of the study.

9. REPORTING OF ADVERSE EVENTS

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

10. REFERENCES

CAPRIE Steering Committee 1996
CAPRIE Steering Committee. A randomised , blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-1339.

García Rodrígues LA and Hernández-Díaz S 2004
García Rodríguez LA, Hernández-Díaz S. Risk of uncomplicated peptic ulcer among users of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs. Am J Epidemiol 2004;159(1):23-31.

Laheij RFJ et al 2003
Laheij RFJ, Van Rossum LGM, Jansen JBMJ, Verheugt FWA. Proton-pump inhibitor therapy for acetylsalicylic acid associated upper gastrointestinal symptoms: a randomized placebo-controlled trial. Aliment Pharmacol Ther 2003;18:109-115.

Laine L 2006
Laine L. Review article: gastrointestinal bleeding with low-dose aspirin – what's the risk? Aliment Pharmacol Ther 2006;24:897-908

Lanas A et al 2006
Lanas A, García-Rodríguez LA, Arroyo MT, Gomollón F, Feu F, González-Pérez A, Zapata E et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut 2006;55:1731-1738.

Patrono C et al 2005
Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Drug Therapy: Low-Dose Aspirin for the Prevention of Atherothrombosis. N Engl J Med 2005; 353:2373-2383.

Silagy CA et al 1993
Silagy CA et al, Adverse effects of low-dose aspirin in a healthy elderly population. Clin Pharmacol Ther 1993;54:84-89.

Shiffman et al 1997
Shiffman et al, A day at a Time: Predicting Smoking Lapse From Daily Urge.. Journal of Abnormal Psychology, 1997;106:104-116.

Stone & Shiffman 2007
Stone A, Shiffman S, Atienza A, Nebeling L. (Eds). The Science of Real-Time Data Capture:Chapter 5, The Analysis of Real-Time Momentary Data: A Practical Guide. Oxford University Press, New York, 2007.

Stone A et al 2003
Stone A, Shiffman S,Schwartz J, Broderick J, and Hufford M**.** Patient compliance with paper and electronic diaries. Controlled Clinical Trials, 24 (2003) 182-199.

Weil J et al 1995
Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. Br Med J. 1995;310:827-830.

Yeomans ND et al 2005
Yeomans ND, Lanas AI, Talley NJ, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. Aliment Pharmacol Ther 2005;22:795-801

Zeger SL et al 1988
Zeger SL, Liang KY, Albert PS. Models for longitudinal data: A generalized estimating equation approach. Biometrics 1988;44(4):1049-1060. (Erratum in Biometrics 1989;45(1):347).

Health Economics/Outcomes Research Methodological Protocol Amendment 1: Appendix A

Drug Substance	Nexium/LDA
Study Code	D961FC00004
Appendix Edition Number	2

Appendix A
Signatures

ASTRAZENECA SIGNATURE

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

I agree to the terms of this amendment.

AstraZeneca Research and Development
site representative

ICON SIGNATURE

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

I agree to the terms of this amendment.

ICON representative

Clinical Study Protocol Amendment

Amendment Number	1
Drug Substance	Nexium, LDA
Study Code	D961FC00004

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

Sponsor:

AstraZeneca R&D Molndal
SE-431 83 Molndal
Sweden

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

The use of the Patient Reported Outcome (PRO) instrument SF-8 will be replaced in all relevant sections of the study protocol with the SF-12 for all scheduled assessments.

Reason for the amendment:

In licensing discussions with the instruments authors, the study team was informed that given recent research the SF-12 would be a more appropriate instrument for assessing the population of interest than the SF-8. No negative consequences for the subjects participating in the study are expected as a result of this change. The change is expected to yield more valid data for the Quality Of Life domain in the study.

Please Note: The described changes in this Amendment affect more than one section in the Clinical Study Protocol (CSP). All sections affected by the change are listed together and ended with “Reason for amendment” and are separated by a dashed line.

Section of protocol affected:

Section 4.2, Table 2.

Previous text:

Table 2 SitePro Survey Domains

Domain	Explanation
Background	Items about gender and LDA use will be entered to facilitate decision on EMA qualification and group.
UGI screening symptoms	Subjects will be asked about UGI symptoms for the past 14 days.
PPI and H2 blocker usage	Evaluates subject use of PPIs and H2 blockers for purposes of EMA qualification, and UGI treatment.
Interaction between UGI and LDA	Evaluates subjects' attribution about UGI symptoms and LDA.
UGI symptoms past 7 days or over past year	Debriefing of UGI symptoms over past 7 days where appropriate, or over past year if no symptoms in past 7 days.
Hospital Anxiety and Depression Scale (HADS)	A subject evaluation on anxiety and depression.
Morisky Medication Taking Behavior Scale	Patients behavior and attributions regarding taking CV medication (modified from original blood pressure medication).
SF-8 Health Survey	**A brief general quality of life assessment.**
Subjective Symptoms Questionnaire (SSA-P)	Assessment of typical side effects from CV medications, including UGI symptoms.

Revised text:

Table 2 SitePro Survey Domains

Domain	Explanation
Background	Items about gender and LDA use will be entered to facilitate decision on EMA qualification and group.
UGI screening symptoms	Subjects will be asked about UGI symptoms for the past 14 days.
PPI and H2 blocker usage	Evaluates subject use of PPIs and H2 blockers for purposes of EMA qualification, and UGI treatment.

Table 2 SitePro Survey Domains

Domain	Explanation
Interaction between UGI and LDA	Evaluates subjects' attribution about UGI symptoms and LDA.
UGI symptoms past 7 days or over past year	Debriefing of UGI symptoms over past 7 days where appropriate, or over past year if no symptoms in past 7 days.
Hospital Anxiety and Depression Scale (HADS)	A subject evaluation on anxiety and depression.
Morisky Medication Taking Behavior Scale	Patients behavior and attributions regarding taking CV medication (modified from original blood pressure medication).
SF-12 Health Survey	**A brief general quality of life assessment.**
Subjective Symptoms Questionnaire (SSA-P)	Assessment of typical side effects from CV medications, including UGI symptoms.

Section of protocol affected:

Appendix C. Section 1.6 SF-8 Health Survey

Previous text:

SF-8™ Health Survey Scoring Demonstration

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

For each of the following questions, please mark an [x] in the one box that best describes your answer.

1. Overall, how would you rate your health during the **past 4 weeks**?

Excellent	Very good	Good	Fair	Poor	Very poor
○	○	○	○	○	○

2. During the **past 4 weeks**, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
○	○	○	○	○

3. During the **past 4 weeks**, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

None at all	A little bit	Some	Quite a lot	Could not do daily work
○	○	○	○	○

4. How much bodily pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very Severe
○	○	○	○	○	○

5. During the **past 4 weeks**, how much energy did you have?

Very much	Quite a lot	Some	A little	None
○	○	○	○	○

6. During the **past 4 weeks**, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all	Very little	Somewhat	Quite a lot	Could not do social activities
○	○	○	○	○

7. During the **past 4 weeks**, how much have you been bothered by **emotional problems** (such as feeling anxious, depressed or irritable)?

Not at all	Slightly	Moderately	Quite a lot	Extremely
○	○	○	○	○

8. During the **past 4 weeks**, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities
○	○	○	○	○

Thank you for completing these questions!

Score the survey | Reset the survey form

Revised Text:

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐

3. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Accomplished less than you would like	☐	☐	☐	☐	☐
Were limited in the kind of work or other activities	☐	☐	☐	☐	☐

4. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Accomplished less than you would like	☐	☐	☐	☐	☐
Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

5. **During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

6. **These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Have you felt calm and peaceful?	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐
Have you felt downhearted and depressed?	☐	☐	☐	☐	☐

7. **During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Thank you for completing these questions!

Reason for Amendment:

In discussions with the instruments authors the study team was informed that the SF-12 would be a more appropriate instrument for assessing the population of interest than the SF-8. No negative consequences for the subjects participating in the study are expected as a result of this change. The change is expected to yield more valid data for the Quality Of Life domain.

Persons who initiated the Amendment:

Clinical Study Team

Health Economics/Outcomes Research Methodological Protocol Amendment No 2 Appendix A

Drug Substance	Nexium/LDA
Study Code	D961FC00004
Edition Number	2
Date	19 June 2008

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

I agree to the terms of this amendment.

AstraZeneca Research and Development
site representative

ICON SIGNATURE

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

I agree to the terms of this amendment.

ICON representative

ASTRAZENECA SIGNATURE(S)

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

I agree to the terms of this amendment.

AstraZeneca Research and Development site representative

Health Economics/Outcomes Research Methodological Clinical Study Protocol Amendment

Amendment Number	2
Drug Substance	Nexium/LDA
Study Code	D961FC00004

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

Sponsor:

AstraZeneca R&D Molndal
S-431 83 Molndal
Sweden

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

1. The inclusion and exclusion criteria for taking the survey are being changed such that LDA-naïve patients (patients that do not have a history of taking low-dose aspirin for cardiovascular disease prevention) will no longer qualify.

2. The inclusion and exclusion criteria for taking the survey are being changed such that patients that have been taking low-dose aspirin for cardiovascular disease prevention for up to five years can be enrolled in the survey.

3. The number of subjects planned for enrollment into the EMA Phase is reduced from 420 to approximately 330.

Reason for the amendment:

1. Enrollment of subjects into the EMA (prospective) phase of the study ends on approximately 15 June 2008, or when the required number of subjects have been enrolled. At that time, a sufficient amount of survey (retrospective) data from this

patient population will have been obtained, so the enrollment of additional LDA-naïve patients solely to take the retrospective survey will not be necessary.

2. To promote the enrollment of patients with a history of taking low-dose aspirin for cardiovascular disease prevention, the time frame for use of low-dose aspirin is being extended from 12 months to 5 years.

3. In the original protocol, the goal was to enroll 120 subjects in EMA Group 2 (”Short-term LDA Users”: Those having used LDA within a 14-day period of taking the survey). Enrollment for Group 2 has proved to be difficult with about 30 subjects expected to be enrolled into Group 2 before the enrollment for the EMA phase is closed. This reduces the number of expected EMA subjects in all groups from 420 to approximately 330.

Section of protocol affected:

3.1 Design and study flow synopsis

Second Paragraph:

Previous text:

In the first stage of the study, approximately 2,000 subjects who have been prescribed LDA usage in the past 12 months, or those about to begin LDA, will complete a one-time in-office survey using an electronic personal digital assistant (PDA) device (termed SitePro).

Revised text:

In the first stage of the study, approximately 2,000 subjects who have been prescribed LDA usage in the past 5 years will complete a one-time in-office survey using an electronic personal digital assistant (PDA) device (termed SitePro). During the first five months of study enrollment, subjects that are about to commence LDA will also complete the in-office survey.

Fourth Paragraph:

Previous text:

A subset of the subjects of whom all complete the survey will be invited to participate in a three (3) month prospective diary period where real-time assessments will be administered using the ecological momentary assessment (EMA) approach. Four hundred, twenty (420) subjects stratified into three groups varying on length of time using LDA will be asked to use an electronic PRO device (ePRO) to record information about their experience with LDA for the period of 3 months. The ePRO device will prompt (via an audible alarm) the subject three (3) times each day and administer questions regarding the subject’s experience with LDA. In

particular, the ePRO device will ask subjects about UGI symptoms, medication use, and about their daily activities and mood. The areas of assessment are listed in Section 4.2.1 (Table 2), and the specific questions are listed in Appendix D. The goal is to obtain EMA data from 350 subjects in the three groups: 200 Naïve LDA users (240 enrolled) who begin LDA use at the time of the study; 100 Short-term LDA users (120 enrolled); and, 50 Long-term LDA users (60 enrolled). A detailed description of the inclusion/exclusion criteria for each EMA group can be found in Section 3.3.3.

Revised text:

A subset of the subjects of whom all complete the survey will be invited to participate in a three (3) month prospective diary period where real-time assessments will be administered using the ecological momentary assessment (EMA) approach. Approximately three hundred, thirty (330) subjects stratified into three groups varying on length of time using LDA will be asked to use an electronic PRO device (ePRO) to record information about their experience with LDA for the period of 3 months. The ePRO device will prompt (via an audible alarm) the subject three (3) times each day and administer questions regarding the subject's experience with LDA. In particular, the ePRO device will ask subjects about UGI symptoms, medication use, and about their daily activities and mood. The areas of assessment are listed in Section 4.2.1 (Table 2), and the specific questions are listed in Appendix D. The goal is to obtain EMA data from 275 subjects in the three groups: 200 Naïve LDA users (240 enrolled) who begin LDA use at the time of the study; 25 Short-term LDA users (approximately 30 enrolled); and, 50 Long-term LDA users (60 enrolled). A detailed description of the inclusion/exclusion criteria for each EMA group can be found in Section 3.3.3.

Section of protocol affected:

3.3.1 Study selection record

Previous text:

Subjects 18 years of age and older, diagnosed as at risk or confirmed with CV disease, and who have been prescribed LDA in the past 12 months or are about to commence LDA will be asked to participate.

Revised text:

Subjects 18 years of age and older, diagnosed as at risk or confirmed with CV disease, and who have been prescribed LDA in the past 5 years will be asked to participate. For the first five months of the study, subjects that are about to commence LDA will also be asked to participate.

Section of protocol affected:

3.3.2.1 inclusion criteria, third bullet point

Previous text:

- Physician prescribed or recommended daily intake of LDA (75-325 mg daily) for cardiovascular disease prevention within the past 12 months, including the day of entry into the study.

Revised text:

- For the first five months of the study: Physician prescribed or recommended daily intake of LDA (75-325 mg daily) for cardiovascular disease prevention within the past 12 months, including the day of entry into the study.
  For the remaining months of the study: Physician prescribed or recommended daily intake of LDA (75-325 mg daily) for cardiovascular disease prevention within the past 5 years.

Health Economics/Outcomes Research Methodological Protocol: Appendix A

Drug Substance	Nexium, LDA
Study Code	D961FC00004
Appendix Edition Number	1

Appendix A
Signatures

ASTRAZENECA SIGNATURE

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

I agree to the terms of this study protocol.

AstraZeneca Research and Development
site representative

ICON SIGNATURE

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI-symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose aspirin

I agree to the terms of this study protocol.

ICON representative

Health Economics/Outcomes Research Methodological Protocol: Appendix C

Drug Substance	Nexium, LDA
Study Code	D961FC00004
Appendix Edition Number	1

Appendix C
Questionnaires

TABLE OF CONTENTS PAGE

1. SITEPRO CROSS-SECTIONAL SURVEY ITEMS AND QUESTIONNAIRES

Text	**Response options**
What is your gender?	Female, Male
Please answer the following questions about gastrointestinal symptoms (GI)	
GI symptoms relate to the stomach and intestines, and include indigestion, abdominal pain and/or heartburn.	
Have you experienced any GI symptoms in the past year?	Yes, No
Did you experience the symptoms only during pregnancy?	Yes, No, Not Applicable
Have you experienced any GI symptoms in the past 14 days?	Yes, No
Thinking about your symptoms over the past 14 days, how often did you have the following:	Yes, No
A burning feeling behind your breastbone?	Yes, No
Pain behind your breastbone?	Yes, No
A burning feeling in the center of the upper stomach?	Yes, No
A pain in the center of the upper stomach?	Yes, No
An acid taste in your mouth?	Yes, No
Unpleasant movement of material upwards from the stomach?	Yes, No

Have you taken PPIs or H2 blocker s for acid suppression in the past year?	PPI, H2 blocker, Both, None
Were the PPIs or H2 blockers recommended or prescribed by a physician?	Yes, No
How many months ago did you start?	0-12 months
Please specify the number of weeks ago you started.	0-4 weeks
Have you taken a PPI or H2 blocker for acid suppression in the past 14 days?	PPI, H2 blocker, Both, None
Are you still taking PPIs or H2 blocker s for acid suppression?	PPI, H2 blocker, Both, None
How long ago did you stop taking PPIs or H2 blockers for acid suppression?	0-12 months
Please specify the number of weeks ago you stopped	0-4 weeks
Please answer the following questions about GI symptoms and use of aspirin for CV prevention	
Did you experience any GI symptoms while taking aspirin for CV prevention?	Yes, No
What do you think caused the GI symptoms?	Activity, Food, Drink, Stress, Aspirin, Other, Not Sure
Did you stop taking aspirin for CV prevention because of GI symptoms?	Yes, No
Please answer the following questions for the past 7 days	

How often have you had difficult getting a good night's sleep because of your symptoms?	Daily, Often, Sometimes, Never
< RDQ for past 7 days>	
<XQS for past 7 days>	
<GSRS for past 7 days>	
Please answer the following questions about yourself	
<HADS>	See questionnnaire
<SSAP>	See questionnaire
<SF-8>	See questionnaire
<Morisky>	See questionnaire
Thank you!	

1.1 The Reflux Disease Questionnaire (RDQ)

The Reflux Disease Questionnaire (RDQ)

Thinking about your symptoms over the past 7 days, how often did you have the following:

A burning feeling behind your breastbone?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Pain behind your breastbone?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

A burning feeling in the center of the upper stomach?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

A pain in the center of the upper stomach?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

An acid taste in your mouth?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Unpleasant movement of material upwards from the stomach?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Alt 1. Thinking about your symptoms over the past 7 days, how would you rate the following:
Alt 2. Thinking about your symptoms over the past 7 days, how would you rate the intensity of the following:

A burning feeling behind your breastbone?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Pain behind your breastbone?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe
A burning feeling in the center of the upper stomach?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

A pain in the center of the upper stomach?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

An acid taste in your mouth?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Unpleasant movement of material upwards from the stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

1.2 eXtraeosophageal QuestionS (XQS)

eXtraeosophageal QuestionS (XQS)

Thinking about your symptoms over the past 7 days, how often did you have the following:

Sleep disturbance?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Chest pain?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Daytime cough?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Nighttime cough?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Hoarseness?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Wheezing?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Difficulty swallowing food through the gullet?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Thinking about your symptoms over the past 7 days, how would you rate the following:

Sleep disturbance?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Chest pain?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Daytime cough?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Nighttime cough?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Hoarseness?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Wheezing?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Difficulty swallowing food through the gullet?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

1.3 The gastrointestinal symptom rating scale (GSRS)

THE GASTROINTESTINAL SYMPTOM RATING SCALE (GSRS)

Please read this first:

This survey contains questions about how you have been feeling and what it has been like DURING THE PAST WEEK. Mark the choice that best applies to you and your situation with an “X” in the box.

1. Have you been bothered by PAIN OR DISCOMFORT IN YOUR UPPER ABDOMEN OR THE PIT OF YOUR STOMACH during the past week?

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

2. Have you been bothered by HEARTBURN during the past week? (By heartburn we mean an unpleasant stinging or burning sensation in the chest.)

 No discomfort at all

 Minor discomfort

 Mild discomfort

 Moderate discomfort

 Moderately severe discomfort

 Severe discomfort

 Very severe discomfort

3. Have you been bothered by ACID REFLUX during the past week? (By acid reflux we mean the sensation of regurgitating small quantities of acid or flow of sour or bitter fluid from the stomach up to the throat.)

 No discomfort at all

 Minor discomfort

 Mild discomfort

 Moderate discomfort

 Moderately severe discomfort

 Severe discomfort

 Very severe discomfort

J. Svedlund, E. Dimenäs, I. Wiklund 1995
GSRS (US-E2)

4. Have you been bothered by HUNGER PAINS in the stomach during the past week? (This hollow feeling in the stomach is associated with the need to eat between meals.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

5. Have you been bothered by NAUSEA during the past week? (By nausea we mean a feeling of wanting to throw up or vomit.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

6. Have you been bothered by RUMBLING in your stomach during the past week? (Rumbling refers to vibrations or noise in the stomach.)

 No discomfort at all

 Minor discomfort

 Mild discomfort

 Moderate discomfort

 Moderately severe discomfort

 Severe discomfort

 Very severe discomfort

J. Svedlund, E. Dimenäs, I. Wiklund 1995
GSRS (US-E2)

7. Has your stomach felt BLOATED during the past week? (Feeling bloated refers to swelling often associated with a sensation of gas or air in the stomach.)

 No discomfort at all

 Minor discomfort

 Mild discomfort

 Moderate discomfort

 Moderately severe discomfort

 Severe discomfort

 Very severe discomfort

8. Have you been bothered by BURPING during the past week? (Burping refers to bringing up air or gas from the stomach via the mouth, often associated with easing a bloated feeling.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

9. Have you been bothered by PASSING GAS OR FLATUS during the past week? (Passing gas or flatus refers to the need to release air or gas from the bowel, often associated with easing a bloated feeling.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

10. Have you been bothered by CONSTIPATION during the past week? (Constipation refers to a reduced ability to empty the bowels.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

11. Have you been bothered by DIARRHEA during the past week? (Diarrhea refers to a too frequent emptying of the bowels.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

12. Have you been bothered by LOOSE STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being loose.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

13. Have you been bothered by HARD STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being hard.)

□ No discomfort at all

□ Minor discomfort

□ Mild discomfort

□ Moderate discomfort

□ Moderately severe discomfort

□ Severe discomfort

□ Very severe discomfort

14. Have you been bothered by an URGENT NEED TO HAVE A BOWEL MOVEMENTduring the past week? (This urgent need to go to the toilet is often associated with a feeling that you are not in full control.)

 No discomfort at all

 Minor discomfort

 Mild discomfort

 Moderate discomfort

 Moderately severe discomfort

 Severe discomfort

 Very severe discomfort

15. When going to the toilet during the past week, have you had the SENSATION OF NOT COMPLETELY EMPTYING THE BOWELS? (This feeling of incomplete emptying means that you still feel a need to pass more stool despite having exerted yourself to do so.)

 No discomfort at all

 Minor discomfort

 Mild discomfort

 Moderate discomfort

 Moderately severe discomfort

 Severe discomfort

 Very severe discomfort

PLEASE CHECK THAT ALL QUESTIONS HAVE BEEN ANSWERED!
THANK YOU FOR YOUR CO-OPERATION.

J. Svedlund, E. Dimenäs, I. Wiklund 1995
GSRS (US-E2)

1.4 Hospital anxiety and depression scale (HADS)

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your clinician to know how you feel. Read each item below and tick the box by the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

1. I feel tense and 'wound up'

__ Most of the time

__ A lot of the time

__ From time to time, occasionally

__ Not at all

2. I still enjoy the things I used to enjoy

__ Definitely as much

__ Not quite so much

__ Only a little

__ Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen

__ Very definitely and quite badly

__ Yes, but not too badly

__ A little, but it doesn't worry me

__ No at all

4. I can laugh and see the funny side of things

__ As much as I always could

__ Not quite so much now

__ Definitely not so much now

__ Not at all

5. Worrying thoughts go through my mind

__ A great deal of the time

__ A lot of the time

__ Not too often

__ Very little

6. I feel cheerful

__ Never

__ Not often

__ Sometimes

__ Most of the time

7. I can sit at ease and feel relaxed

__ Definitely

__ Usually

__ Not often

__ Not at all

8. I feel as if I am slowed down

__ Nearly all the time

__ Very often

__ Sometimes

__ Not at all

9. I get a sort of frightened feeling like ‘butterflies’ in the stomach

__ Not at all

__ Occasionally

__ Quite often

__ Very often

10. I have lost interest in my appearance

__ Definitely

__ I don’t take as much care as I should

__ I may not take quite as much care

__ I take just as much care as ever

11. I feel restless as if I have to be on the move

__ Very much indeed

__ Quite a lot

__ Not very much

__ No at all

12. I look forward with enjoyment to things

__ As much as I ever did

__ Rather less than I used to

__ Definitely less than I used to

__ Hardly at all

13. I get sudden feelings of panic

__ Very often indeed

__ Quite often

__ Not very often

__ Not at all

14. I can enjoy a good book or radio or television programme

__ Often

__ Sometimes

__ Not often

__ Very seldom

NOW CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS

(UK-English)

1.5 Subjective symptoms questionnaire (SSA-P)

SUBJECTIVE SYMPTOMS QUESTIONNAIRE
(SSA-P)

The purpose of this questionnaire is to find out how you are feeling, so it is just as important to indicate how well you are feeling as how ill you are feeling.

It is also important that you answer all questions regardless of whether you think the symptoms are mild or not.

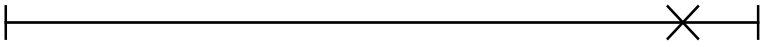
How to fill in the form:

Answer each question by putting a cross (X) on the line depending on how you have been feeling during the past week.

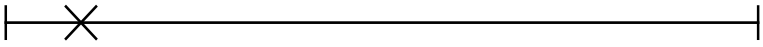
Example:

Have you been UNHAPPY during the past week?

If you have been rather unhappy, put a cross towards the right end of the line.

Very happy  Very unhappy

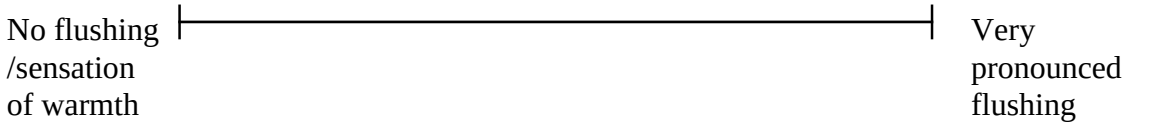
If you have been rather happy, put a cross towards the left end of the line.

Very happy  Very unhappy

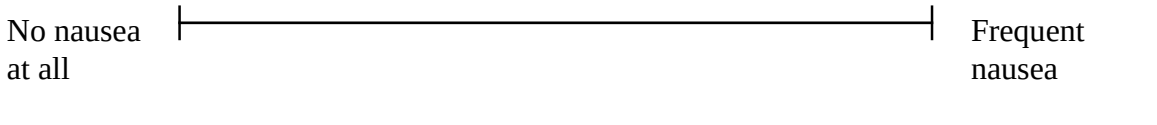
If neither happy nor unhappy fits in with how you have been feeling, put your cross in the middle of the line.

Very happy  Very unhappy

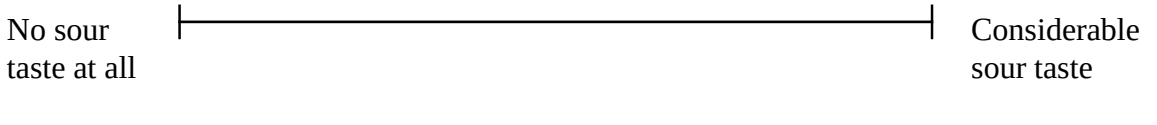
1. Have you been bothered by FLUSHING (REDNESS) OR SENSATION OF WARMTH IN THE SKIN during the past week?



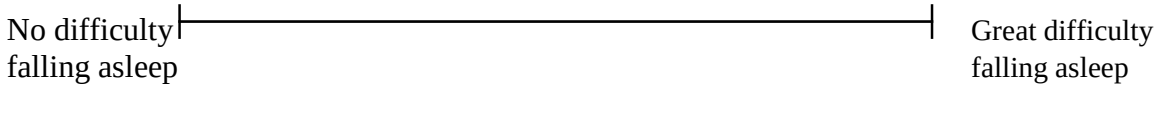
2. Have you been troubled by NAUSEA during the past week?



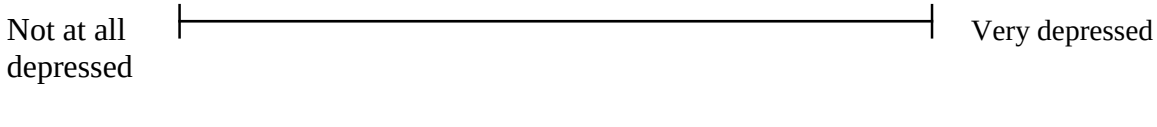
3. Have you been troubled with SOUR TASTE IN THE MOUTH OR THROAT during the past week?



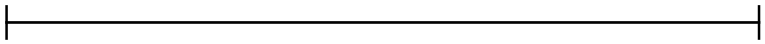
4. Have you had TROUBLE FALLING ASLEEP during the past week?



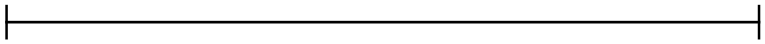
5. Have you been DEPRESSED during the past week?



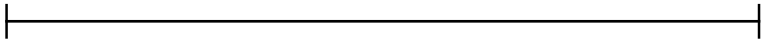
6. Have you felt TIRED during the past week?

Not at all tired  Very tired

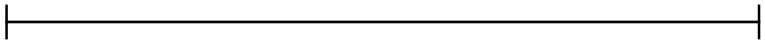
7. Have you been bothered by DIZZINESS during the past week?

No dizziness at all  Very pronounced dizziness

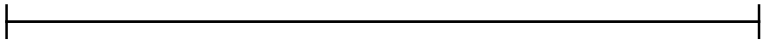
8. Have you felt DROWSY during the past week?

Not at all drowsy  Very drowsy

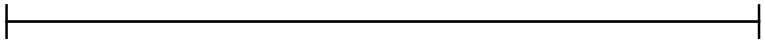
9. Have you been troubled by HEADACHES during the past week?

No headaches  Frequent headaches

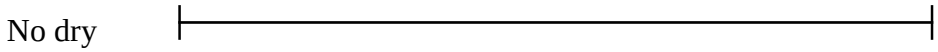
10. Have you been troubled by SWEATING during the past week?

No abnormal sweating  Excessive sweating

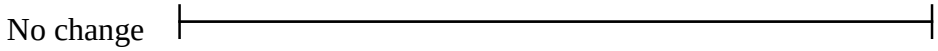
11. Have you had SWOLLEN ANKLES OR FEET during the past week?

No swollen ankles/feet  Very swollen ankles/feet

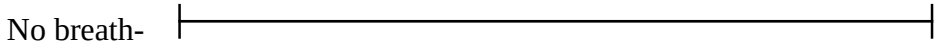
12. Have you been troubled by DRY MOUTH during the past week?



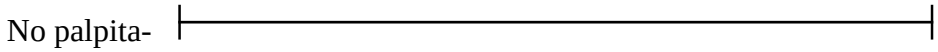
13. Have you experienced that FOOD TASTED DIFFERENTLY during the past week?



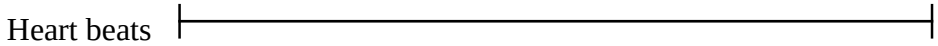
14. Have you suffered from BREATHLESSNESS during the past week?



15. Have you had any trouble with PALPITATIONS during the past week?



16. Have you had any problem with your HEART BEATING RAPIDLY during the past week?



17. Have you had any problem with your HEART BEATING SLOWLY during the past week?

Heart beats normally — Heart beats very slowly

18. Have you suffered from DIARRHEA during the past week?

No diarrhea at all — Very severe diarrhea

19. Have you suffered from CONSTIPATION during the past week?

No consti-pation at all — Very severe constipation

20. Have you been bothered by PASSING GAS during the past week?

No gas at all — Severe gas

21. Have you had any NIGHTMARES during the past week?

No night-mares — A lot of nightmares

22. Have you felt NERVOUS OR ANXIOUS during the past week?

Not nervous/ anxious at all — Very nervous/ anxious

23. Have you suffered from ITCHINESS during the past week?

No itchiness at all — Very pronounced itchiness

24. Have you experienced TREMBLING HANDS during the past week?

No sign of trembling hands — A lot of trouble with trembling hands

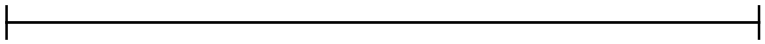
25. Have you noticed a decrease in your SEXUAL FUNCTION during the past week?

No decrease in sexual function — Major decrease in sexual function

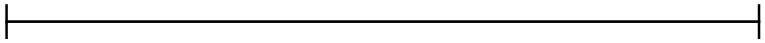
26. Have you felt any INTEREST IN OR DESIRE FOR SEX during the past week?

Considerable interest in or desire for sex — No interest in or desire for sex

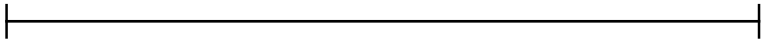
27. Have you felt COLD in normal conditions during the past week?

Not felt cold  Often felt cold

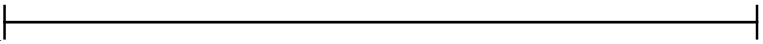
28. Have you been bothered by COLD HANDS OR FEET during the past week?

No cold hands/feet  Cold hands/ feet frequently

29. Have you suffered from a DRY COUGH during the past week?

Not coughed at all  Very severe cough

30. Have you suffered from STOMACH ACHE OR PAIN during the past week?

No stomach ache/pain at all  Very severe stomach ache/ pain

31. Have you been bothered by WAKING UP TOO EARLY during the past week?

Not woken up early at all — Have woken up very early

32. Have you had difficulty in CONCENTRATING on normal activities during the past week?

No difficulty in concentrating — Very pronounced difficulty in concentrating

33. Have you been bothered by MUSCULAR WEAKNESS during the past week?

No muscular weakness — Very pronounced muscular weakness

34. Have you felt DIZZY ON SUDDENLY CHANGING YOUR POSITION during the past week?

No dizziness on changing position — Very dizzy on changing position

35. Have you suffered from any IRRITATION OF THE EYES during the past week?

No irritation at all — Eyes very irritated

36. Have you had any problem with BLURRED VISION during the past week?

No blurred vision at all — Very severe blurred vision

37. Have you had any trouble with BUZZING OR RINGING IN YOUR EARS during the past week?

No buzzing/ ringing in the ears — Severe buzzing/ ringing in the ears

38. Have you had any problem with NUMBNESS IN YOUR FINGERS OR TOES during the past week?

No loss of feeling/ numbness — Very pronounced loss of feeling/ numbness

39. Have you suffered from CALF PAIN OR CRAMP during the past week?

No calf pain/cramp — Very severe calf pain/cramp

40. How has your APPETITE been during the past week?

Very good appetite ⊢——————————————⊣ No appetite at all

41. Have you had any TROUBLE WITH YOUR MUSCLES AND/OR JOINTS during the past week?

No trouble at all ⊢——————————————⊣ A lot of trouble

42. Have you been experiencing URGENCY OF URINATION during the past week?

No urgency of urination ⊢——————————————⊣ Frequent urgency of urination

PLEASE CHECK THAT ALL QUESTIONS HAVE BEEN ANSWERED!

THANK YOU FOR YOUR CO-OPERATION.

1.6 SF-8tm Health Survey Scoring Demonstration

SF-8™ Health Survey Scoring Demonstration

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

For each of the following questions, please mark an [x] in the one box that best describes your answer.

1. Overall, how would you rate your health during the **past 4 weeks**?

Excellent	Very good	Good	Fair	Poor	Very poor
○	○	○	○	○	○

2. During the **past 4 weeks**, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
○	○	○	○	○

3. During the **past 4 weeks**, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

None at all	A little bit	Some	Quite a lot	Could not do daily work
○	○	○	○	○

4. How much bodily pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very Severe
○	○	○	○	○	○

5. During the **past 4 weeks**, how much energy did you have?

Very much	Quite a lot	Some	A little	None
○	○	○	○	○

6. During the **past 4 weeks**, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all	Very little	Somewhat	Quite a lot	Could not do social activities
○	○	○	○	○

7. During the **past 4 weeks**, how much have you been bothered by **emotional problems** (such as feeling anxious, depressed or irritable)?

Not at all	Slightly	Moderately	Quite a lot	Extremely
○	○	○	○	○

8. During the **past 4 weeks**, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities
○	○	○	○	○

Thank you for completing these questions!

Score the survey | Reset the survey form

1.7 Morisky Medication Taking Behavior Scale

Morisky Medication Taking Behavior Scale

1. Do you sometimes forget to take your CV medications? (Check one)

___Yes

___No

2. People sometimes miss taking their CV medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your CV medications? (Check one)

___Yes

___No

3. Have you ever cut back or stopped taking your CV medication without telling your doctor, because you felt worse when you took it? (Check one)

___Yes

___No

4. When you travel or leave home, do you sometimes forget to bring along your high blood pressure medication? (Check one)

___Yes

___No

5. Did you take your CV medications yesterday? (Check one)

___Yes

___No

6. When you feel like your symptoms are under control, do you sometimes stop taking your CV medicine? (Check one)

___Yes

___No

7. Taking CV medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan? (Check one)

___Yes

___No

8. How often do you have difficulty remembering to take all your CV medications? (Check one)

___Never or rarely

___Once in a while

___Sometimes

___Usually

___All of the time

Health Economics/Outcomes Research Methodological Protocol: Appendix D

Drug Substance	Nexium, LDA
Study Code	D961FC00004
Appendix Edition Number	1

Appendix D
ePRO-EMA Diary Self Initiated Assessment

ePRO-EMA Diary Self Initiated Assessment

Text	**Response options**
About your episode:	
How long ago did it end?	<1 minute, 2-5 minutes, >5 minutes
How long did it last?	0-480 minutes
Where were you most during the episode?	Home, Workplace, Other's home, Bar, Restaurant, Vehicle, Outside, Casino, Other
What were you doing during the episode?	Working/chores, Inactive/leisure, Interacting with others, Eating/drinking (15 min), Between activities, Other activities
Type of work?	Job, School, House/Personal, Other
Type of inactivity/leisure?	Media, Hanging out, Hobbies, Sports/Exercise, Reading, Waiting, Doing nothing, Other
Type of interaction with others?	Socializing, For business, Household issues, Arguing, Other interaction
What eating or drinking?	Meal, Snack, Caffeinated drink, Non-caffeinated drink, Alcohol
Thinking about your symptoms during the episode, how would you rate the following:	

A burning feeling behind your breastbone?	Did not have, Very mild, Mild, Moderate, Moderately sever, Severe
Pain behind your breastbone?	Did not have, Very mild, Mild, Moderate, Moderately sever, Severe
A burning feeling in the center of the upper stomach?	Did not have, Very mild, Mild, Moderate, Moderately sever, Severe
A pain in the center of the upper stomach?	Did not have, Very mild, Mild, Moderate, Moderately sever, Severe
An acid taste in your mouth?	Did not have, Very mild, Mild, Moderate, Moderately sever, Severe
Unpleasant movement of material upwards from the stomach?	Did not have, Very mild, Mild, Moderate, Moderately sever, Severe
Were you bothered by NAUSEA? (By nausea we mean a feeling of sickness that may lead to retching and vomiting.)	No discomfort at all, minor discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, sever discomfort, very severe discomfort
Did your stomach feel BLOATED? (Feeling bloated refers to swelling often associated with a sensation of gas or air in the stomach.)	No discomfort at all, minor discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, sever discomfort, very severe discomfort

Did your stomach felt BLOATED? (Feeling bloated refers to swelling often associated with a sensation of gas or air in the stomach.)	No discomfort at all, minor discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, sever discomfort, very severe discomfort
Did you feel CRAMPS in your stomach/belly?	No discomfort at all, minor discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, sever discomfort, very severe discomfort
Thinking about your emotions during the episode…	
Able to focus?	NO!!, no??, yes??, YES!!
Alert?	NO!!, no??, yes??, YES!!
Angry/frustrated?	NO!!, no??, yes??, YES!!
Bored	NO!!, no??, yes??, YES!!
Calm/relaxed?	NO!!, no??, yes??, YES!!
Difficulty concentrating?	NO!!, no??, yes??, YES!!

Enthusiastic?	NO!!, no??, yes??, YES!!
Happy?	NO!!, no??, yes??, YES!!
Irritable?	NO!!, no??, yes??, YES!!
Miserable?	NO!!, no??, yes??, YES!!
Nervous/tense?	NO!!, no??, yes??, YES!!
Quiet/sleepy?	NO!!, no??, yes??, YES!!
Restless?	NO!!, no??, yes??, YES!!
Sad?	NO!!, no??, yes??, YES!!
Overall feeling?	Very bad, Bad, Neutral, Good, Very good
Arousal/energy level?	Very low, Low, Moderate, High, Very high
Please answer these questions about what you did about your episode/	

What did in response to the episode?	Nothing, Change Acitivity, Eat, Drink, Medication, Contact doctor/hospital
What medication did you take?	PPIs, H2, drink, over-the-counter
What do you think caused the episode?	Nothing, Activity, Food, Drink, Mood, Stress
Thank you!	

Morning Assessment

Text	**Response options**
ABOUT LAST NIGHT…	
Cigarettes smoked but NOT entered?	0-10
Trouble falling asleep?	NO!!, no??, yes??, YES!!
Slept well?	NO!!, no??, yes??, YES!!
Number of awakenings?	0-20
Since last report	
Did you experience a GI episode?	Yes, No
Thinking about your emotions since your last report…	
Able to focus?	NO!!, no??, yes??, YES!!
Alert?	NO!!, no??, yes??, YES!!
Angry/frustrated?	NO!!, no??, yes??, YES!!
Bored	NO!!, no??, yes??, YES!!
Calm/relaxed?	NO!!, no??, yes??, YES!!

Difficulty concentrating?	NO!!, no??, yes??, YES!!
Enthusiastic?	NO!!, no??, yes??, YES!!
Happy?	NO!!, no??, yes??, YES!!
Irritable?	NO!!, no??, yes??, YES!!
Miserable?	NO!!, no??, yes??, YES!!
Nervous/tense?	NO!!, no??, yes??, YES!!
Quiet/sleepy?	NO!!, no??, yes??, YES!!
Restless?	NO!!, no??, yes??, YES!!
Sad?	NO!!, no??, yes??, YES!!
Overall feeling?	Very bad, Bad, Neutral, Good, Very good
Arousal/energy level?	Very low, Low, Moderate, High, Very high
Thank you!	

Afternoon Assessment

Text	**Response options**
Since last report	
Did you experience a GI episode?	Yes, No
Where were you most?	Home, Workplace, Other's home, Bar, Restaurant, Vehicle, Outside, Casino, Other
What were you doing?	Working/chores, Inactive/leisure, Interacting with others, Eating/drinking (15 min), Between activities, Other activities
Type of work?	Job, School, House/Personal, Other
Type of inactivity/leisure?	Media, Hanging out, Hobbies, Sports/Exercise, Reading, Waiting, Doing nothing, Other
Type of interaction with others?	Socializing, For business, Household issues, Arguing, Other interaction
What eating or drinking?	Meal, Snack, Caffeinated drink, Non-caffeinated drink, Alcohol

Thinking about your emotions since your last report…	
Able to focus?	NO!!, no??, yes??, YES!!
Alert?	NO!!, no??, yes??, YES!!
Angry/frustrated?	NO!!, no??, yes??, YES!!
Bored	NO!!, no??, yes??, YES!!
Calm/relaxed?	NO!!, no??, yes??, YES!!

Difficulty concentrating?	NO!!, no??, yes??, YES!!
Enthusiastic?	NO!!, no??, yes??, YES!!
Happy?	NO!!, no??, yes??, YES!!
Irritable?	NO!!, no??, yes??, YES!!
Miserable?	NO!!, no??, yes??, YES!!
Nervous/tense?	NO!!, no??, yes??, YES!!

Quiet/sleepy?	NO!!, no??, yes??, YES!!
Restless?	NO!!, no??, yes??, YES!!
Sad?	NO!!, no??, yes??, YES!!
Overall feeling?	Very bad, Bad, Neutral, Good, Very good
Arousal/energy level?	Very low, Low, Moderate, High, Very high
Thank you!	

Evening Assessment

Text	**Response options**
Answer the following about the time since your last evening report…	
Since last evening report	
What medications did you take?	Low dose aspirin, Other heart medication, GI medication
Did you visit the doctor or hospital?	Doctor, Emergency room, Hospital
Was it a planned visit?	Yes, No
Are you still in the hospital?	Yes, No
Why did you visit the hospital or doctor?	Heart related problems, GI problems, other
Able to control important things?	NO!!, no??, yes??, YES!!
Able to handle personal problems?	NO!!, no??, yes??, YES!!

Nervous/stressed?	NO!!, no??, yes??, YES!!
Things going your way?	NO!!, no??, yes??, YES!!
Unexpected event upset you?	NO!!, no??, yes??, YES!!
Upset by things out of your control?	NO!!, no??, yes??, YES!!
Since last report	
Did you experience a GI episode?	Yes, No
Where were you most?	Home, Workplace, Other's home, Bar, Restaurant, Vehicle, Outside, Casino, Other

What were you doing?	Working/chores, Inactive/leisure, Interacting with others, Eating/drinking (15 min), Between activities, Other activities
Type of work?	Job, School, House/Personal, Other
Type of inactivity/leisure?	Media, Hanging out, Hobbies, Sports/Exercise, Reading, Waiting, Doing nothing, Other
Type of interaction with others?	Socializing, For business, Household issues, Arguing, Other interaction
What eating or drinking?	Meal, Snack, Caffeinated drink, Non-caffeinated drink, Alcohol
Thinking about your emotions since your last report…	
Able to focus?	NO!!, no??, yes??, YES!!

Alert?	NO!!, no??, yes??, YES!!
Angry/frustrated?	NO!!, no??, yes??, YES!!
Bored	NO!!, no??, yes??, YES!!
Calm/relaxed?	NO!!, no??, yes??, YES!!
Difficulty concentrating?	NO!!, no??, yes??, YES!!
Enthusiastic?	NO!!, no??, yes??, YES!!

Happy?	NO!!, no??, yes??, YES!!
Irritable?	NO!!, no??, yes??, YES!!
Miserable?	NO!!, no??, yes??, YES!!
Nervous/tense?	NO!!, no??, yes??, YES!!
Quiet/sleepy?	NO!!, no??, yes??, YES!!
Restless?	NO!!, no??, yes??, YES!!

Sad?	NO!!, no??, yes??, YES!!
Overall feeling?	Very bad, Bad, Neutral, Good, Very good
Arousal/energy level?	Very low, Low, Moderate, High, Very high