Clinical Study Protocol

Drug Substance AZD3355

Study Code D9120C00027

Date

Validation of patient-reported outcome measures for the assessment of GERD symptoms and their subsequent impact on patients with a partial response to PPI treatment in a two part multi-center phase IIA study including a four week randomised, double-blind, placebo-controlled parallel-group treatment period with AZD3355, 65 mg bid as add-on treatment to a PPI

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

Validation of patient-reported outcome measures for the assessment of GERD symptoms and their subsequent impact on patients with a partial response to PPI treatment in a two part multi-center phase IIA study including a four week randomised, double-blind, placebo-controlled parallel-group treatment period with AZD3355, 65 mg bid as add-on treatment to a PPI

Principal Investigator

Study site(s) and number of patients planned

This study will be carried out in approximately 500 patients in Part 1 and 450 patients in Part 2 from approximately 80 sites in the USA.

Study period	**Phase of development**
Estimated date of first patient enrolled	Phase IIA
Estimated date of last patient completed	

Objectives

Validation Objectives

- To determine which symptoms in the modified RDQ electronic diary (e-diary) are relevant for the target patient population
- To establish the validity, reliability, and ability to detect change (responsiveness) of the modified RDQ e-diary in the target patient population
- To establish the clinically meaningful change of the modified RDQ e-diary in the target patient population
- To determine which symptoms or symptom domains from the modified RDQ e-diary will form the basis for the primary endpoint in future studies in the target patient population
- To determine a responder definition in the target patient population
- To investigate the validity, reliability and ability to detect change (responsiveness) of the modified QOLRAD for assessing the impact of GERD symptoms in the target patient population
- To investigate the validity of alternative diary based PRO instruments for assessing the impact of GERD symptoms in the target patient population

Additional Objectives

- To assess the safety and tolerability during 4 weeks treatment with AZD3355 65 mg bid as add-on treatment to a PPI in partial responders to PPI treatment who still experience GERD symptoms

Study design

This PRO validation study consists of two parts: Part 1 will determine the key symptom clusters and establish the validity and reliability of the modified RDQ e-diary for patients who are partial responders to PPI treatment but still experiencing GERD symptoms. Part 2 will use a randomised double-blind, placebo-controlled parallel-group design with AZD3355 as an add-on to optimised[a] PPI treatment. The clinically meaningful change of the modified RDQ

[a] Prior to enrolment, the patients must be continuously treated with an unchanged PPI treatment with doses within the FDA approved label for any GERD indication. The patient must be treated with the PPI for at least 4 weeks prior to enrolment. An optimised PPI treatment is a treatment which according to the investigator's judgment can not be further improved by changing brand or dosing of the PPI during the 4 weeks prior to enrolment. Patients with recently diagnosed reflux (erosive) esophagitis must have completed the prescribed treatment period with up to 8 weeks PPI treatment.

e-diary will be established and a responder definition will be derived in the target patient population.

Study population

The study population in this study are partial responders to PPI treatment who still experience at least mild intensity GERD symptoms on at least 3 of the past 7 days. Patients will be males and females aged 18 and 70 years, inclusive. The patients must have a history of GERD symptoms for at least 6 months (need not to be consecutive) and must be on optimised PPI treatment. Non-responders to PPI treatment will be excluded based on evaluation by the investigator.

Investigational product, dosage and mode of administration

Oral administration of AZD3355 65 mg capsules twice daily (bid).

Comparator, dosage and mode of administration

Oral administration of matching placebo capsules, indistinguishable in appearance from the AZD3355 capsules.

Duration of treatment

The study consist of two parts; Part 1 is a run-in period of 8-12 days; Part 2 is a treatment period with AZD3355 bid or placebo of 4 weeks, and a follow-up period of 12-16 days for safety assessment.

Outcomes

- **Patient-reported outcome (PRO) instruments**
  - Modified RDQ screening instrument (7 day recall)
  - Modified RDQ e-diary
  - "Most troublesome symptoms"
  - Gastrointestinal Symptom Rating Scale (GSRS)
  - SF-36(tm) version 2 acute recall period (SF-36v2 acute)
  - Modified QOLRAD - Questionnaire for patients with symptoms of heartburn or regurgitation
  - Impact of Symptoms e-diary items
  - MOS Sleep Scale
  - Treatment Satisfaction Questionnaire – GERD (TSQ-G)

- Overall Treatment Evaluation (OTE)
- "Sufficient symptom control"
- Hospital Anxiety and Depression Scale (HADS)

- **Safety**
  - Adverse events (AEs)
  - Laboratory values
  - Vital signs (blood pressure [BP] and pulse)
  - Physical examination
  - ECG/dECG

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 study protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in section 4.4.1.1)
ALT (SGPT)	Alanine transaminase (serum glutamic pyruvic transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomic Therapeutic Chemical
AZDD	AstraZeneca Drug Dictionary
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
COC	Combined Oral Contraceptive
CHMP	Committee for Medical Products for Human Use
COOL	Clinical Operations On Line (Web based data capture system)
CPK (CK)	Creatine phosphokinase (creatine kinase)
CSA	Clinical Study Agreement
CRO	Contract Research Organisation
DBP	Diastolic Blood Pressure
DUS	Disease Under Study
ECG	Electrocardiogram
dECG	Digital electrocardiogram
eCRF	Electronic Case Report Form
e-diary	Electronic diary
ePRO	Electronic Patient-Reported Outcome(s)
Ethics Committee	Synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
FDA	Food and Drug Administration
Free T4	Free thyroxine
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
GSRS	Gastrointestinal Symptom Rating Scale
HADS	Hospital Anxiety and Depression Scale
HRT	Hormonal Replacement Therapy
hs-CRP	High-sensitivity C-reactive protein
IBS	Irritable Bowel Syndrome
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IUD/IUS	IntraUterine Device/IntraUterine System
ISF	Investigators Study File
LES	Lower esophageal sphincter
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimal Important Change
MID	Minimal Important Difference
MCHC	Mean corpuscular haemoglobin concentration
MCS	Mental Component Summary
MCV	Mean corpuscular volume
MOS	Medical Outcomes Study
NSAID	Non-Steroid Anti-Inflammatory Drugs
OAE	Other significant adverse event (ie adverse events of particular clinical importance, other than SAEs and those AEs leading to early discontinuation of the patient from study treatment; see definition in section 4.4.1.1)
OTC	Over-the-counter
OTE	Overall Treatment Evaluation
Partial responder	Patients who have some relief, but still experience GERD symptoms despite PPI treatment
PCS	Physical Component Summary
PFI	Pill Free Interval
PREGREP	Pregnancy Outcome Report
PGWB	Psychological General Well-Being
PPI	Proton Pump Inhibitor
PRN	Pro Re Nata
PRO(s)	Patient-Reported Outcome(s)

Abbreviation or special term	Explanation
PUD	Peptic Ulcer Disease
QOLRAD	Quality of Life in Reflux and Dyspepsia
QLABS	Quintiles Laboratories Ltd
QTc	Corrected QT interval
QTcF	Corrected QT interval according to Fridericia's formula
RBC	Red blood cell (erythrocyte)
RDQ	Reflux Disease Questionnaire
SAE	Serious adverse event (see definition in section 4.4.1.1).
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDV	Source Data Verification
SF-36v2 acute	The 36-item Short Form Health Survey (version 2 - acute)
Study population	Partial responders to PPI treatment who still experience GERD symptoms (at least 3 days of at least *mild* GERD symptoms during the last week) despite PPI treatment
Target patient population	Partial responders to PPI treatment who still experience GERD symptoms (at least 3 days of at least *moderate* GERD symptoms during the last week) despite PPI treatment
TSH	Thyroid-stimulating hormone
TSQ-G	Treatment Satisfaction Questionnaire-GERD
WBDC	Web-based data capture
WBC	White blood cell (leukocyte)

1. INTRODUCTION

1.1 Background

Gastroesophageal Reflux Disease (GERD) is a common condition with the predominant symptoms of heartburn and/or regurgitation (Vakil et al 2006), with these symptoms occurring at least weekly in 10-20% of the population in the Western world (Dent et al 2005). While acid suppressive therapy with proton pump inhibitors (PPIs) has proved to be effective in the treatment of GERD, there are unmet medical needs since approximately 40% of patients continue to experience GERD symptoms despite PPI treatment (Fass et al 2005, Jones et al 2007). These partial responders to PPI treatment continue to experience GERD symptoms despite PPI treatment with a negative impact on patients' lives (Wiklund at al 2003).

The remaining symptoms may be explained by various factors, eg remaining esophageal acid exposure, esophageal hypersensitivity, weakly acidic or weakly alkaline reflux. The lower esophageal sphincter (LES) provides the major pressure barrier between the stomach and the esophagus and consequently constitutes an important factor for prevention of reflux. Combined motility and pH-metric studies have shown that transient LES relaxations (TLESRs) triggered by gastric distension account for approximately 80% of all reflux episodes, both in healthy volunteers and patients with GERD without esophagitis (Dent et al 1988, Holloway et al 1990).

AZD3355, a selective $GABA_B$ receptor agonist, is a reflux inhibitor that targets TLESRs. It is being developed as add-on treatment to PPI therapy for patients who are partial responders to PPI treatment with persistent GERD symptoms. A recently completed study in patients with GERD symptoms despite PPI treatment has shown that AZD3355 65 mg bid as add-on treatment to a PPI was well tolerated and significantly reduced the primary GERD symptoms, ie heartburn (burning feeling behind the breastbone) and regurgitation (unpleasant movement of material upwards from the stomach), in comparison to placebo (D9120C00011). These symptoms were assessed using an e-diary version of the Reflux Disease Questionnaire (RDQ), a patient-reported outcome (PRO) measure designed and validated to measure symptoms of GERD.

Efficacy evaluation using PROs as outcome measures is well supported in various therapeutic areas. Moreover, PROs have been used as primary outcomes in areas such as acute pain, irritable bowel syndrome, migraine and osteoarthritis. The use of PROs is also supported in a regulatory context by the Food and Drug Administration (FDA) as outlined in the "Guidance for industry: patient-reported outcome measures: use in medical product development to support labelling claims: draft guidance" (FDA 2006). In this draft guidance, PRO is defined as any report coming directly from patients (ie study subjects) about a health condition and its treatment. Further, it states that measures that do not directly capture the impact of treatment on how a patient survives, feels or functions are surrogate measures of treatment benefit.

A substantial portion of the GERD population has non-erosive reflux disease and therefore diagnosis can not be confirmed by endoscopy or other objective measures (Fass et al 2001) and must thus be based on symptoms reported by patients. In addition, patient-reported data has been suggested to more reliably reflect the response to treatment of GERD than assessment of symptoms by the clinician (McColl et al 2005).

It is becoming commonly accepted that the diagnosis and management of GERD can be based on patients' report of symptoms (Jones et al 2007). This has been formally addressed in a new definition and classification of GERD developed by an International Consensus Group (Vakil et al 2006).The results were first presented at the World Congress of Gastroenterology in Montreal. Specifically, the definition concludes that GERD diagnosis is best based on a "patient-centered definition of troublesome symptoms". It was further noted that such a definition bridges cultures and countries, may simplify disease management, facilitate collaborative research and increase the generalizability of studies.

Heartburn and regurgitation have been found to be the two typical symptoms of GERD (Vakil et al 2006). Recently performed cognitive interviews and focus groups confirmed the presence and importance of these two symptoms in patients with GERD symptoms despite PPI treatment (Report from Mapi Values). In addition, these two symptoms were improved in study D9120C00011 in patients treated with AZD3355. In patient interviews and focus groups, other symptoms that might be of relevance in the treatment of GERD were found. These additional symptoms have been reported in the literature as associated with GERD in general. However, the relevance of these in partial responders to PPI treatment is not known. Therefore, the additional symptoms have been added to the existing RDQ, to derive a modified RDQ e-diary which will be evaluated for appropriate measurement properties in this study. In addition, a definition of clinically meaningful change and a responder definition will be established for the target patient population, ie partial responders to PPI treatment who still experience GERD symptoms.

Given the negative impact of GERD symptoms on patients' daily lives, it is important not only to measure treatment induced symptom change but also the impact of this change on patients' lives. A review of existing PRO instruments addressing the impact of GERD symptoms was performed to select the most appropriate instrument for the target patient population (Report from PRO Consulting). The findings indicated that the heartburn version of the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire was the most appropriate starting point. In order to better fit the target patient population, the symptom descriptions of the QOLRAD were revised based on input from patient interviews and focus groups (Report from Mapi Values), to comprise the modified QOLRAD.

1.2 Rationale

This PRO validation study will provide the empirical evidence for selecting the primary and secondary endpoints and measures for the planned phase IIB and III development program for AZD3355, in partial responders to PPI treatment with persistent GERD symptoms.

The target patient population for the future AZD3355 program are patients who experience at least moderate intensity GERD symptoms on at least 3 of the past 7 days. However, the study population in the validation protocol also will comprise patients who experience mild symptom intensity. A broader group of patients is being evaluated in the current study to support the identification and validation of symptom clusters in the target patient population.

The information obtained from this study will establish which modifications in the PRO instruments are relevant for both assessment of GERD symptoms and impact of GERD symptoms on patients' lives in the target patient population. Subsequently, the relevant measurement properties of the modified RDQ e-diary and the modified QOLRAD will be established in the target patient population. Additionally, the clinically meaningful change of the modified RDQ e-diary as well as a responder definition will be established.

Once the measurement properties, clinically meaningful change and a responder definition are established with the PRO measures, the remaining AZD3355 clinical development program will utilize these measures in the phase IIB and III studies.

2. STUDY OBJECTIVES

2.1 Objectives related to validation

- To determine which symptoms in the modified RDQ e-diary are relevant for the target patient population
- To establish the validity, reliability, and ability to detect change (responsiveness) of the modified RDQ e-diary in the target patient population
- To establish the clinically meaningful change of the modified RDQ e-diary in the target patient population
- To determine which symptoms or symptom domains from the modified RDQ e-diary will form the basis for the primary endpoint in future studies in the target patient population
- To determine a responder definition in the target patient population
- To investigate the validity, reliability and ability to detect change (responsiveness) of the modified QOLRAD for assessing the impact of GERD symptoms in the target patient population
- To investigate the validity of alternative diary based PRO instruments for assessing the impact of GERD symptoms in the target patient population

2.2 Additional Objectives

- To assess the safety and tolerability during 4 weeks treatment with AZD3355 65 mg bid as add-on treatment to a PPI in partial responders to PPI treatment who still experience GERD symptoms

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

The study will use a double-blind, placebo-controlled, randomised, parallel group design and will be conducted in multiple sites in the USA.

The patients in this study must have a history of GERD symptoms for at least 6 months (need not to be consecutive) and must be on optimised[b] PPI treatment. Non-responders to PPI treatment will be excluded (based on evaluation by the investigator).

In order to meet the objectives of the study, the study will have two parts, see Figure 1. The anticipated numbers of patients to screen is approximately 600 patients in order to enrol approximately 500 patients in Part 1. This is expected to generate 450 eligible patients in Part 2, so as to randomise 225 patients per arm.

Part 1

To be eligible for inclusion in Part 1 of the study, the patients must have reported in the modified RDQ screening instrument using 7 days recall of symptoms:

- A frequency of a burning feeling behind the breastbone of at least 3 days over the past 7 days and a rating of its intensity as at least mild

  and/or

[b] Prior to enrolment, the patients must be continuously treated with an unchanged PPI treatment with doses within the FDA approved label for any GERD indication. The patient must be treated with the PPI for at least 4 weeks prior to enrolment. An optimised PPI treatment is a treatment which according to the investigator's judgment can not be further improved by changing brand or dosing of the PPI during the 4 weeks prior to enrolment. Patients with recently diagnosed reflux (erosive) esophagitis must have completed the prescribed treatment period with up to 8 weeks PPI treatment.

- A frequency of unpleasant movement of material upwards from the stomach of at least 3 days over the past 7 days and a rating of its intensity as at least mild

At visit 1 after enrolment into Part 1 the patients will fill out a number of PRO questionnaires at the clinic (see Table 1) and be instructed to start recording GERD symptoms and other associated symptoms twice daily in an e-diary for 8-12 days. During this period of time patients must continue their optimised PPI treatment and will also have rescue medication (GELUSIL® antacid/anti-gas tablets) available. The last 7 days of symptom recording in Part 1 will be used to evaluate whether the patient meets the criteria for randomisation into Part 2.

Approximately 40 enrolled patients at pre-identified study sites, who consent to participate in two cognitive interviews, will have appointments during Part 1 and Part 2 of the study, see section 4.3.

Part 2

The eligibility for randomisation into Part 2 will be based on twice daily recording of symptoms during the last 7 days in Part 1 in the modified RDQ e-diary. During this period the patient must have recorded on at least 3 days a symptom intensity of at least mild of one or both of these symptoms;

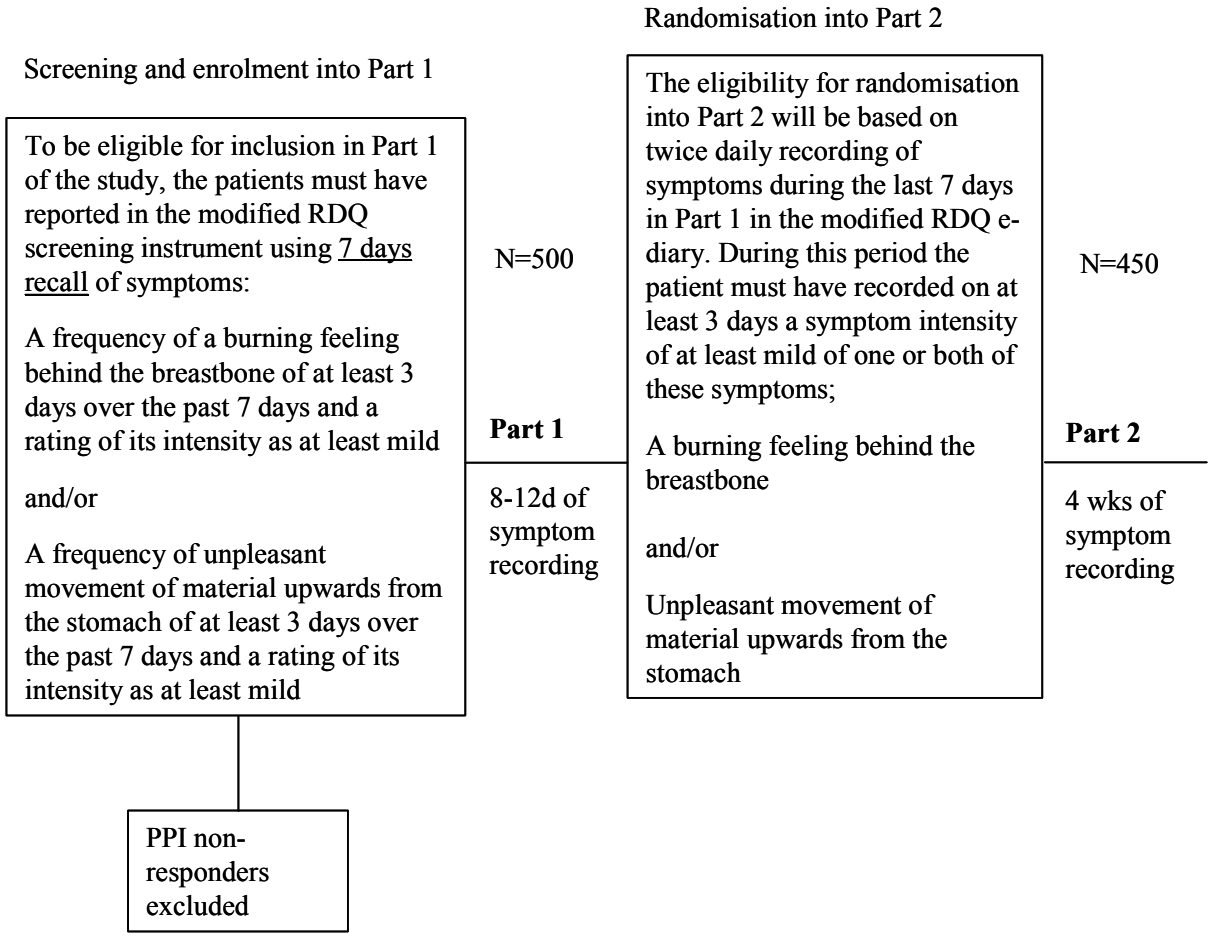
- A burning feeling behind the breastbone

and/or

- Unpleasant movement of material upwards from the stomach

During Part 2, each patient will be given AZD3355, 65 mg bid or placebo for 4 weeks as an add-on treatment to his or her PPI. The patients must continue their optimised PPI treatment (from Part 1) and will also have rescue medication (GELUSIL® antacid/anti-gas tablets) available. The patients will continue to record their GERD symptoms twice daily in the e-diary.

Figure 1 Selection of study population



[1] Prior to enrolment, the patients must be continuously treated with an unchanged PPI treatment with doses within the FDA approved label for any GERD indication.The patient must be treated with the PPI for at least 4 weeks prior to enrolment. An optimised PPI treatment is a treatment which according to the investigator's judgment can not be further improved by changing brand or dosing of the PPI during the 4 weeks prior to enrolment. Patients with recently diagnosed reflux (erosive) esophagitis must have completed the prescribed treatment period with up to 8 weeks PPI treatment.

Study flow

All patient-reported data will be collected via electronic devices. An e-diary device will be used for the twice daily symptom registration and will be brought home by the patients. A similar electronic device will be used at the clinic for completion of the additional PRO instruments at each visit. SAEs will be collected during the entire study period and AEs will be collected and followed up after randomisation (see section 4.4.1.1). Concomitant medication will be monitored at all visits.

Part 1

Visit 1: (12 to 8 days prior to randomisation) After giving written informed consent, patients will receive training in how to complete PRO instruments and use the site-based electronic device. Thereafter, they will complete the modified RDQ screening instrument. If the patient fulfils the inclusion criteria of the modified RDQ, additional PRO instruments (see Table 3) will be completed prior to any further assessment.

Each patient will then undergo a physical examination, an extended laboratory screen, ECG, supine BP and pulse, medical and surgical history, weight and height, and will be evaluated for all inclusion and exclusion criteria. Women of childbearing potential will undergo a urine pregnancy test.

Patients will receive training in how to use the e-diary device, and will start recording in the e-diary in the evening on the day of visit 1. They will also receive a selected over-the-counter (OTC) antacid as rescue medication (GELUSIL® antacid/anti-gas tablets) to use as needed if they experience GERD symptoms during the study. The patients will be instructed to bring any empty GELUSIL® antacid/anti-gas tablets cartons and/or blister packs, as well as any unused rescue medication, with them to visit 2.

Patients from selected sites, who consent to participate in the cognitive interviews, will be scheduled for the first cognitive interview (at visit 2 with a time window of up to 5 days prior to visit 2) and the second cognitive interview (at visit 5 with a time window of up to 7 days prior to or 2 days after visit 5).

ePRO data collection during Part 1

During Part 1, patients will enter twice daily e-diary recordings of GERD symptoms, impact of symptoms and the use of GELUSIL® antacid/anti-gas tablets. Throughout the study, the study staff will monitor the e-diary compliance and call each non-compliant patient in order to support and resolve possible issues.

Part 2

Visit 2. (Day 1)Additional PRO instruments (see Table 3) will be completed by all patients prior to any further assessment. The modified RDQ e-diary registrations during the last 7 days will be used to evaluate if the patient meets the criteria for being randomised into Part 2.

For each eligible patient the investigator will check the laboratory results of serum creatinine, AST, ALT, potassium, magnesium and other serum electrolytes from visit 1. Women of childbearing potential will undergo a second urine pregnancy test.

If scheduled, the first cognitive interview will be performed at visit 2 (with a time window of 5 days prior to visit 2). When an interview is conducted on the day of visit 2, then the interview will be carried out after the completion of the PRO instruments , and prior to clinical assessments.

Patients still eligible for the study will then undergo a physical examination, weight and a laboratory screen. Further, an e-diary device check (eg, battery status, data transfer) and e-diary compliance review will be done.

Prior to the first dose of investigational product, a dECG will be performed followed by the measurement of a supine and standing BP and pulse. The patients fulfilling all of the randomisation criteria will then be randomised to either placebo or AZD3355 treatment 65 mg bid for 4 weeks in the proportion 1:1. The patient will then take the first dose of the investigational product at the site. One hour after the first dose a dECG will be performed again, followed by the measurement of a supine and standing BP and pulse.

Investigational product will be dispensed at the visit sufficient for treatment until visit 4. The patients will be instructed to take 1 capsule in the morning after symptom registration in the e-diary but approximately 30 minutes before breakfast and 1 capsule in the evening approximately 30 minutes before their main meal, with a glass of water. Rescue medication (GELUSIL® antacid/anti-gas tablets) could still be used if necessary.

The patients will also be instructed to bring any empty bottles, cartons and/or blister packs, as well as any unused investigational products and rescue medication, with them to visit 4.

ePRO data collection during Part 2

Randomised patients will continue twice daily e-diary recordings of GERD symptoms, impact of symptoms and use of GELUSIL® antacid/anti-gas tablets until the morning on the day of visit 5. The study staff will continue the regularly monitoring of the e-diary compliance as during Part 1.

Visit 3 (phone visit). 5 to 9 days after randomisation, the study staff at the clinic will phone the patient, ask about drug compliance and discuss the e-diary device and e-diary compliance.

Visit 4. 12 to 16 days after randomisation, patients should complete additional PRO instruments prior to any further assessment (see Table 1), dECG, supine and standing BP and pulse, laboratory screen, e-diary device check and e-diary compliance review and drug accountability. Drug will be dispensed for the last two treatment weeks. A second carton of rescue medication (GELUSIL® antacid/anti-gas tablets) will be dispensed for continued use as necessary.

The patients will also be instructed to bring any empty bottles, cartons and/or blister packs, as well as any unused investigational products and rescue medication, with them to visit 5.

Visit 5. 26 to 30 days after randomisation, patients should complete additional PRO instruments (see Table 3) prior to any further assessment, physical examination, weight, dECG, supine and standing BP and pulse, laboratory screen, e-diary device check and e-diary compliance review and drug accountability. The patient will take the last dose of study drug the evening before the day of visit 5, the optimised PPI treatment will continue. The e-diary recordings of symptoms will end in the morning the day of visit 5 and the e-diary device will be collected at the site.

The patients will be instructed to bring any empty GELUSIL® antacid/anti-gas tablets cartons and/or blister packs, as well as any unused rescue medication, with them to visit 6.

If scheduled, the second cognitive interview will be performed at visit 5 (with a time window of up to 7 days prior to or 2 days after visit 5). When an interview is conducted on the day of visit 5, then the interview will be carried out after the completion of the PRO instruments, and prior to clinical assessments.

Visit 6. 12-16 days after visit 5, a follow up visit is done. Each patient will undergo a physical examination, an extended laboratory screen, dECG, supine and standing BP and pulse. Women of childbearing potential will undergo a urine pregnancy test.

Figure 2 Study flow chart

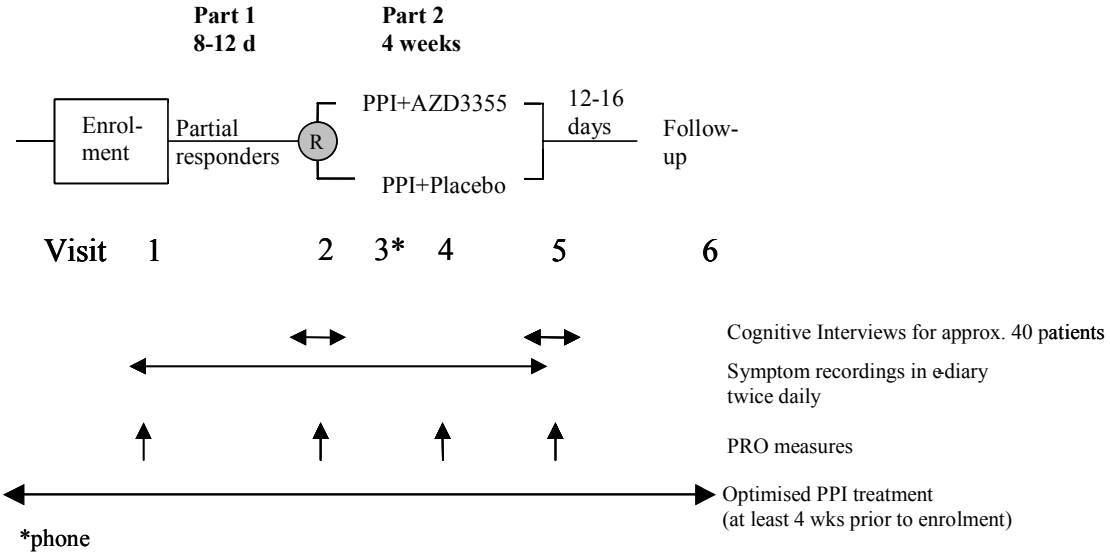


Table 1 Study plan						
	Part 1	**Part 2 (treatment period)**				**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Visit Description	Enrolment	Randomisation	Phone contact		End of treatment	Study completion
Visit Window (No. Weeks ± No. Days)	**12 to 8 days prior to randomisation**	**Day 1**	**5 to 9 days after randomisation**	**12 to 16 days after randomisation**	**26 to 30 days after randomisation**	**12 to 16 days after visit 5**
Informed consent	X					
Medical and surgical history	X					
Inclusion/exclusion criteria	X	X				
Weight	X	X			X	
Height	X					
Physical examination	X	X			X	X
dECG[f] (performed in triplicate within 5 minutes)	X	X[e]		X	X	X
Supine and standing BP and pulse	X[d]	X[e]		X	X	X
Laboratory screen[f]	X [a]	X		X	X	X [a]
Urine pregnancy test (women of childbearing potential) [f]	X	X				X
Dispense rescue medication	X	X		X	X	
Dispense blinded Investigational Product		X		X		
Prior/Concomitant medication	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Serious adverse events	X	X	X	X	X	X
ePRO training	X	X				
Site-based PRO assessment (See Table 3)	X	X		X	X	
Assignment of e-diary device	X					
Twice daily e-diary recordings[b] (See Table 4)	X[b]---------	----------	----------	----------	X[b]	
Check of e-diary and review of e-diary compliance		X	X	X	X	
Collection of e-diary device					X	

Table 1 Study plan						
	Part 1	**Part 2 (treatment period)**				**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Visit Description	Enrolment	Randomisation	Phone contact		End of treatment	Study completion
Visit Window (No. Weeks ± No. Days)	**12 to 8 days prior to randomisation**	**Day 1**	**5 to 9 days after randomisation**	**12 to 16 days after randomisation**	**26 to 30 days after randomisation**	**12 to 16 days after visit 5**
Cognitive interviews	---	X[c]		------	X[c]--	

[a] Extended laboratory screen
[b] Patients make twice daily e-diary recordings, starting before bedtime in the evening after visit 1 and ending in the morning the day of visit 5.
[c] Approximately 40 patients will be invited to participate in face to face cognitive interviews to further examine their experience of GERD symptoms (at visit 2 with a time window of up to 5 days prior to visit 2 at visit 5 with a time window of up to 7 days prior to or 2 days after visit 5).
[d] At visit 1 only supine BP and pulse
[e] At visit 2 dECG, supine and standing BP and pulse before and 1 hour after first dose of investigational product.
[f] For early discontinuation visits, after randomisation, a dECG, extended laboratory screen, including a urine pregnancy test for women of childbearing potential should be done.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

Patient-reported data has been suggested to more reliably reflect the response to treatment of GERD than assessment of symptoms by the clinician (McColl et al 2005). Patient-reported symptoms are best evaluated based on daily recordings (Fass et al 2005, Fass 2007), for example using electronic diaries. Electronic capture of PRO (ePRO) data ensures that diary entries are not made in advance or retrospectively (Stone et al 2002) and makes it possible to continuously review the compliance of the reporting.

In order to meet the objectives of the study, the study will have two parts.

In Part 1 of the study, the symptom pattern in the target patient population will be assessed during an 8-12 day period using an e-diary. These will include both RDQ items and additional symptom items derived from patients in this target patient population using patient interviews and focus groups (Report from Mapi Values). The analysis of the symptom data from Part 1 will determine the key symptom cluster to be analysed in Part 2 of the study, and establish validity and reliability of the modified RDQ e-diary. The validity and reliability of the modified QOLRAD will also be investigated in this part. Further, the last 7 days of symptom recording in Part 1 will be used to determine eligibility for randomisation into Part 2 of the study.

The aim of Part 2 of the study is to establish validity and the ability to detect change (responsiveness) of the modified RDQ e-diary in the target patient population and subsequently clinically meaningful change. In addition, the reliability and ability to detect change (responsiveness) of the modified QOLRAD will be assessed in the target patient population. In addition to the evaluation of the PRO instruments above, additional PRO instruments will be used as references. The most troublesome symptom question will be used to support which symptoms in the modified RDQ e-diary are relevant to the target patient population. The GSRS, SF-36 v2 acute, OTE, TSQ-G, sufficient symptom control and HADS will be used as references in the assessment of validity, reliability, ability to detect change (responsiveness) or clinically meaningful change.

Patients will continue the twice daily e-diary entries throughout the study up until visit 5.

Currently, there are no approved add-on medications for this particular patient segment. A treatment effect is needed to accomplish the study aims, therefore, AZD3355, a Reflux Inhibitor in clinical development by AstraZeneca will be used, as this compound has been shown in a phase IIA study to have a positive effect in patients with GERD symptoms despite PPI treatment.

Experience from earlier studies in GERD with PPIs indicates that 4 weeks is long enough to show efficacy in the treatment of symptoms. The rationale for the decision to use AZD3355 65 mg bid for 4 weeks in this study is that this dosage has been shown to be effective in reducing GERD symptoms and well tolerated in a previous study (D9120C00011) of 122 Patients with GERD symptoms despite PPI treatment.

The inclusion and exclusion criteria in the study are aimed at recruiting partial responders to PPI treatment who still experience GERD symptoms, without other significant or unstable medical conditions that could compromise patient safety, influence the ability to comply with study procedures or interfere with the interpretation of efficacy and safety data.

3.2.2 Risk/benefit and ethical assessment

In total, AZD3355 has been administered to 364 healthy volunteers in 13 studies. The drug has been given as single oral doses in the range of 0.1 mg/kg to 2.5 mg/kg, and as repeated oral doses up to 500 mg and as an intravenous infusion of 0.2 mg/kg. In a recently completed study in patients with GERD symptoms despite PPI treatment, 122 patients were randomised to treatment with AZD3355 65 mg twice daily during 4 weeks (D9120C00011). One patient has reported SAEs during active treatment with AZD3355 65 mg twice daily (headache and hypertension), not considered to be drug related by the investigator. Adverse events have generally been mild to moderate and no specific safety concerns have been raised.

Mild to moderate short lasting paresthesiae without other neurological findings have occurred in some healthy volunteers and study patients, most frequently during the first day of administration. Pre-study medical history will be collected specifically to identify information regarding previous episodes of paresthesiae, and patients with current neurological disorders will be excluded. All patients reporting paresthesiae during the study will undergo neurological examination by the investigator. Patients experiencing paresthesiae for 7 consecutive days meet criteria for discontinuation from study treatment, and will be examined by a board certified neurologist.

A Thorough QT study (D9120C00012) was performed, however, this study failed to exclude an effect of AZD3355 on the prolongation of the QTc interval. Therefore until the potential effect of AZD3355 on the QTc interval has been fully evaluated, digital ECG monitoring (dECG) and additional exclusion criteria, have been included in this clinical study.

Since $GABA_B$ agonists may interfere with the barostatic reflex, hemodynamic effects of a dose of 500 mg AZD3355 have been assessed in a TILT study in healthy volunteers (D912C00021). A single dose of 500 mg was given orally and the head-up tilt was performed at predicted C_{max}. Results showed that subjects have a shorter head-up endurance time when taking AZD3355 as compared to placebo. However, the evaluation thus far does not indicate an effect of AZD3355 on the baroreflex itself but rather indicates signs of peripheral vasodilatation.

Until possible implications of potential cardiovascular effects of AZD3355 for patients at therapeutic dose levels have been further evaluated, patients with a history of severe orthostatic reactions, syncope, supine systolic BP below 110 mmHg, any heart disease or other predisposing factors for cardiac arrhythmia, will not be included in the clinical trials. In the previous patient study (D9120C00011), in which similar exclusion criteria were applied, no obvious effects related to low BP or cardiac arrhythmias were observed. In addition, in the current study monitoring with dECG and supine and standing BP and pulse measurements will be done during the treatment period and safety follow-up.

No genotoxicity of AZD3355 has been observed in pre-clinical studies. Animals studies have not shown adverse effects on fertility or embryofetal development. However, because no data exists on embryofetal development in humans, women of childbearing potential must use an adequate highly effective contraceptive method to be eligible for the study. The pharmacokinetics and pharmacodynamics of oral contraceptives has not been studied when administered in combination with AZD3355. However *in vitro* data indicate that AZD3355 is neither an inhibitor nor inducer of CYP 3A4. Hence, there is no indication that AZD3355 should affect the metabolism of hormonal contraceptives.

There are no direct advantages for the patients participating in this study. Discomfort and risks to the participating patients in this study are judged to be small and justified by the benefit of a potential new effective treatment for partial responders to PPI treatment with persistent GERD symptoms.

3.3 Selection of study population

The study population in this study are partial responders to PPI treatment who still experience at least mild intensity GERD symptoms on at least 3 of the past 7 days. Patients will be males and females aged 18 and 70 years, inclusive. The patients must have a history of GERD symptoms for at least 6 months (need not to be consecutive) and must be on optimised[c] PPI treatment. Helicobacter pylori serology test will be done at enrolment for baseline characteristics and both Helicobacter pylori positive and negative patients will be included.

Patients who have not responded at all to PPI treatment will not be part of the study population since many of these complete non responders may have other causes for their symptoms other than gastroesophageal reflux. Non-responders to PPI treatment will be excluded based on the evaluation by the investigator.

Patients who still experience GERD symptoms while on PPI therapy continue to have the predominant symptoms of heartburn and regurgitation (Charbel et al 2005, Mainie et al 2006, Zerbib et al 2006). This was confirmed in a recent set of cognitive interviews and focus groups (Report from Mapi Values) in patients with GERD symptoms despite PPI treatment.

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[c] Prior to enrolment, the patients must be continuously treated with an unchanged PPI treatment with doses within the FDA approved label for any GERD indication. The patient must be treated with the PPI for at least 4 weeks prior to enrolment. An optimised PPI treatment is a treatment which according to the investigator's judgment can not be further improved by changing brand or dosing of the PPI during the 4 weeks prior to enrolment. Patients with recently diagnosed reflux (erosive) esophagitis must have completed the prescribed treatment period with up to 8 weeks PPI treatment.

Thus, the selection of patients for the study will be based on the frequency and intensity of the patient-reported symptoms “a burning feeling behind the breastbone” (heartburn) and “unpleasant movement of material upwards from the stomach” (regurgitation).

Patient’s eligibility for Part 1 will be based on symptom frequency and intensity using a 7 day recall report in the modified RDQ screening instrument, whereas eligibility for Part 2 will be based on twice daily symptom recording in the modified RDQ e-diary during the last 7 days of Part 1.

At the enrolment visit, visit 1, the RDQ answers will be based on a 7 day recall (retrospectively) and it is not possible to know on which specific days the various symptoms had occurred. Reporting 2 days of “a burning feeling behind the breastbone” and 1 day of “unpleasant movement of material upwards from the stomach” could actually reflect only 2 days of symptoms if “a burning feeling behind the breastbone” and “unpleasant movement of material upwards from the stomach” occurred on the same day. Therefore to achieve a total of 3 days of symptoms there must be a report of either 3 days of “a burning feeling behind the breastbone” **or** 3 days of “unpleasant movement of material upwards from the stomach”.

However, before randomisation, at visit 2, symptom recording will be done daily in the e-diary and data for all symptoms will be available making it possible to identify specific days in which only one or both “a burning feeling behind the breastbone” and “unpleasant movement of material upwards from the stomach” symptoms occurred (e.g. 3 separate days with any of; only “a burning feeling behind the breastbone”, only “unpleasant movement of material upwards from the stomach”, or a combination of “a burning feeling behind the breastbone” and “unpleasant movement of material upwards from the stomach” would make the patient eligible for randomisation.

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled ie, a patient screening log. This information is necessary to establish that the study population was selected without bias.

3.3.2 Inclusion criteria

For inclusion into **Part 1** the patients must fulfil all of the following criteria:

1. Provision of signed informed consent

2. Able to read and write in US English and able to use the electronic devices

3. Have reported in the modified RDQ screening instrument (7 day recall) a burning feeling behind the breastbone with a frequency of at least 3 days over the past 7 days and with at least mild intensity and/or unpleasant movement of material upwards from the stomach with a frequency of at least 3 days over the past 7 days and with at least mild intensity (An algorithm which is programmed in the site based electronic device, will determine eligibility automatically).

4. Male or female, age 18-70 years, inclusive. Females must not be of childbearing potential or must have used one of the following highly effective contraceptive methods for the last 3 months.

   - No childbearing potential criteria
     - Post-menopausal females (either of);
       - Females >50 and have been amenorrheic for 12 months or more and have not used exogenous hormonal treatment
       - Females >50 and have been amenorrheic for 12 months or more, following cessation of all exogenous hormonal treatments
       - Females >57 regardless of whether they are on Hormonal Replacement Therapy (HRT)
     - Permanent sterilisation by hysterectomy and/or bilateral oophorectomy
   - Women of childbearing potential must use one of the following highly effective contraceptive methods
     - Bilateral tubal ligation/occlusion
     - IUD/IUS (copper banded coils or progestin-releasing [Mirena®] progesterone)
     - High dose progestin as depot injection or subcutaneous implant (eg, DepoProvera®, Inplanon®)
     - Combined oral contraceptive (COC) with fixed doses of estrogen and progestin if already using the TriCycle regime
       - TriCycle regime means instead of taking a single 3-week course of COC pills followed by 1 week off COC, the patient takes 3 or 4 courses together (ie, 9-12 weeks of daily COC) with, between each 9-12 week cycle, a shortened 4-day pill free interval (PFI) rather than the usual 7-day PFI. Note: Triphasic pills, which have different strength pills in the same pack, are not considered highly effective and are therefore excluded from this instruction

5. BMI 18.5 – 35.0, inclusive

6. Have at least 6 months history of GERD symptoms (need not to be consecutive)

7. Continuously treated with optimised unchanged PPI treatment with doses within the FDA approved label for any GERD indication during the last 4 weeks before enrolment. (An optimised PPI treatment is a treatment which according to the investigators judgment can not be further improved by changing brand or dosing of the PPI.)

   – Patients with a history of recently diagnosed reflux (erosive) esophagitis (Los Angeles grade A-D) must have been continuously treated with a PPI during at least 8 weeks before enrolment (during the last 4 weeks of treatment for esophagitis and/or GERD and prior to enrolment, the PPI therapy was considered optimised and in accordance with local labelling)

8. Have a PPI prescription with refills that covers the study period or if an over-the-counter (OTC) PPI, instructions for continued daily use over the study period. Note: Prilosec OTC is acceptable and considered to be embraced by the general label for omeprazole (all other OTC PPIs that may become available during the course of the study are also acceptable and their use will follow the labelling of their prescription counter-part)

For inclusion into **Part 2** of the study patients must fulfil the following inclusion criteria *(ie applicable at visit 2)*:

9. Have reported in the modified RDQ e-diary during the last 7 days of Part 1, a burning feeling behind the breastbone and/or unpleasant movement of material upwards from the stomach of at least mild intensity during at least 3 days. (An algorithm based on the e-diary recordings will determine whether the patient fulfils the criteria, and this result will be presented in a Web report).

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Patients that have not experienced any GERD symptoms improvement at all after PPI treatment

2. PPI treatment with doses outside the FDA approved label for GERD and GERD related indications. Note: Twice daily (bid) dosing is not allowed.

3. Working night shifts during the period of the study

4. Unstable or clinically significant cardiovascular, respiratory, renal, hepatic, metabolic, psychiatric, other clinical disorders, or other gastrointestinal and esophageal disorders besides GERD.

- Patients with uncomplicated, well controlled hypertension (SBP ≤160 and DBP ≤90) and patients with uncomplicated, well controlled Diabetes Mellitus as judged by the investigator could be included.

- Clinical significant is defined as disorders that could compromise patients' safety or interfere with the evaluation of the study as judged by the investigator.

5. Current neurological disorders including nerve compression syndromes/rhizopathy (patients with well controlled migraine and other headache disorders could be included)

6. History of or current malignant disease

7. History or signs or symptoms of any heart disease (including ischemic heart disease, congestive heart failure, cardiac arrhythmias, congenital long QT syndrome) or persons with clinically significant ECG abnormalities as determined by the investigator or QTcF >450 ms

8. History of electrolyte imbalances

9. History of clinically significant orthostatic reaction or syncope

10. Supine systolic BP below 110 mm Hg

11. Prior surgery of the upper GI tract (open, endoscopic and laparoscopic surgery on the esophagus, the stomach and the duodenum with the exception of oversewing or endoscopic treatment of bleeding ulcer)

12. History of severe allergy/hypersensitivity or symptoms/signs of ongoing allergy/hypersensitivity

13. Need for concomitant medication with the following:

    - Drugs that may interfere with the pharmacodynamic effect of the Investigational Product (eg, Baclofen)

    - Drugs that may influence gastrointestinal symptoms

        - PPI (except the PPI that was optimized prior to study enrolment and will be taken during the study, neither the dose or brand of PPI should be changed during the study)

        - Antacids (other than rescue medication [GELUSIL® antacid/anti-gas tablets] supplied in the study)

        - H_2 receptor antagonists

- Sucralfate
- Alginates
- Tegaserod
- Domperidone
- Metoclopramide
- Erythromycin
- Drugs with significant anticholinergic effect (eg anticholinergics used in gastro-intestinal disorders; anticholinergics used for Parkinson's disease; anticholinergics used for urine bladder disorders; tricyclic antidepressants)
- Non-steroid anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors (with the exception of occasional use up to 1 day/week)
- Acetylsalicylic acid (ASA) >162 mg
- Biphosphonates
- Antineoplastic drugs

- Drugs that may prolong the QT interval (see Appendix N)
- Drugs that have a narrow therapeutic window (eg warfarin, digoxin, phenytoin, carbamazepine)

14. History of drug addiction, drug abuse (including cannabinoids) or alcohol abuse or other circumstances which in the investigators judgment may compromise the patient's ability to comply with the study requirements
15. Pregnant or breast feeding females
16. Any other condition which in the opinion of the investigator would render the patient unsuitable for inclusion in the study
17. Blood donation within 8 weeks prior to the first dose of the investigational product
18. Involvement in the planning or conduct of the study
19. Administration of any investigational product within 8 weeks prior to administration of the first dose of the investigational product

20. Previous enrolment or randomisation of treatment in the present study

In addition to the criteria above, patients will be assessed at visit 2 for the following criteria, which will be a reason for exclusion from randomisation into **Part 2** of the study, but not from completing Part 1:

21. S-creatinine >1.2 times upper limit of normal at visit 1

22. AST or ALT >3 times upper limit of normal at visit 1

23. Serum potassium below the lower reference range at visit 1, serum magnesium below the lower reference range at visit 1, and other clinically significant electrolyte imbalances at visit 1, as judged by the investigator

24. QTcF >450 ms, reported on any of the three dECG printouts recorded pre-dose at visit 2, as reviewed by the investigator

3.3.4 Restrictions

As safety laboratory monitoring will be done through out the study and blood loss might impact laboratory results the patients must abstain from blood donation while participating in the study. The patient should not change the PPI treatment **and avoid changes** of other medications during the study.

Patients should not receive eradication therapy for Helicobacter pylori during the study.

In addition, patients should not plan surgeries during the study and any other period that in the opinion of the investigator would interfere with their participation and collection of study data.

3.3.5 Precautions to minimise risk of pregnancy

3.3.5.1 Assurance of non-pregnancy at study start

For women of childbearing potential two negative urine pregnancy tests are required prior to the first dose and will be performed by the site at visit 1 and visit 2.

Before enrolment, females will have had to be on a stable and approved birth control method for a minimum of 3 months.

3.3.5.2 Monitoring during and after study

- Urine pregnancy test at visit 1, visit 2 and visit 6.
- Vomiting within 3 hours of taking oral contraception does pose a risk equivalent to a missed pill and patients should follow the guidelines for a missed pill

In addition, consent information will explicitly state that only limited data on the risks in pregnancy are available and that women of childbearing potential will need to commit to complying with the measures described in this protocol in order to be included in the study.

3.3.6 Early discontinuation of patients from treatment or assessment

3.3.6.1 Criteria for early discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are as follows:

- Voluntary early discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to the protocol as judged by the investigator and/or AstraZeneca
- Incorrect enrolment ie, the patient does not to meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Adverse Event (AE) (see section 4.4.1.1)
    - Patients experiencing paresthesiae daily for at least 7 consecutive days
    - Patients experiencing clinically significant orthostatic reaction or syncope
    - Patients with QTcF >500 ms

3.3.6.2 Procedures for early discontinuation before randomisation

For enrolled but not randomised patients, the following modules in the electronic Case Report Form (eCRF) must be entered at minimum:

- Demography (DEM) module
- Eligibility criteria (CRIT) module
- If SAE criteria was fulfilled, the Adverse Events (AELOG) module and Serious Adverse Event Report (SAECOOL) module must be completed
- Study termination (TERM) module
- Electronic signature

In addition, patients who have discontinued after visit 1 but before randomisation, should complete all ePRO assessments according to visit 2 randomisation, see Table 3. The e-diary device must be returned by the patient and reviewed and drug accountability for GELUSIL® antacid/anti-gas tablets should be completed.

3.3.6.3 Procedures for early discontinuation after randomisation

Patients who discontinue after randomisation should always be asked about the reason(s) for their early discontinuation and the presence of any AEs. All patients should be seen and assessed by an investigator. For early discontinuation visits, assessments according to end-of-treatment visit (visit 5) should be done, including patients completing the visit 5 ePRO assessments. In addition, a dECG, an extended laboratory screen and a urine pregnancy test for women of childbearing potential, should be performed. All patients should be strongly encouraged to attend the follow-up visit. AEs and/or SAEs, including QTcF prolongations, must be followed up. The e-diary device and investigational product must be returned by the patient, drug accountability, and an e-diary device check must be done. Patients withdrawn from the investigational product due to daily paresthesiae for at least 7 consecutive days must be referred to a board certified neurologist for examination and followed-up by the investigator 12-16 days after discontinuation of investigational product (visit 6). A copy of the report from the neurologist must be provided to AstraZeneca.

3.4 Treatments

3.4.1 Identity of investigational product and comparators

Table 2 Identity of AZD3355 and placebo

Treatment	Dosage form and strength	Manufacturer	Formulation number
AZD3355	IR capsule, 65 mg	AstraZeneca R&D Mölndal, Sweden	H 1838-02-01
Placebo	Capsule	AstraZeneca R&D Mölndal, Sweden	H 1990-01-01

3.4.2 Identity of Rescue Medication –

Generic name: GELUSIL® antacid/anti-gas tablets

Dosage form: tablets

Manufacturer: to be provided to the study site through AstraZeneca and/or designee.

3.4.3 Doses and treatment regimens

At visit 2, patients will be randomised to receive either AZD3355 capsule 65 mg or placebo capsule bid for 4 weeks. Each patient kit contains 2 bottles, each filled with 36 capsules. The patients will receive one bottle at visit 2 and the second bottle at visit 4.

One carton of rescue medication, GELUSIL® antacid/anti-gas tablets, will be provided at the enrolment visit (visit 1). According to the instructions on the label, one carton is a sufficient amount for the patient to continue up to visit 4. A second carton of rescue medication will be dispensed at visit 4 for continued use as necessary until the study completion (visit 6). The patient must be instructed to use the rescue medication only if the patient experiences symptoms of GERD, not for prophylactic reasons. The number of GELUSIL® antacid/anti-gas tablets taken should not exceed what is prescribed in the label, and the number of tablets should be recorded in the e-diary. The rescue medication will be sourced by AstraZeneca IPS US (Wilmington, Delaware) and distributed by a third-party vendor, AccuLogix (Bristol, Pennsylvania).

3.4.4 Labelling

AstraZeneca will be responsible for the packaging and labelling of the investigational product. All supplies and labels will be prepared in accordance with Good Manufacturing Practices (GMP) and local regulatory guidelines and include the following information:

- Name of sponsor and address
- Pharmaceutical dosage form, route of administration, quantity of dosage units
- Name and strength of product
- Study code
- Enrolment code/Randomisation code
- Treatment period
- Dosage instructions
- Order number
- Storage conditions
- Local Country’s caution statement

The investigational products will be sent to AstraZeneca IPS US, who will forward the medication to the third party vendor for distribution to the sites.

The bottles of AZD3355 capsules and matching placebo for visit 2 through visit 5 will be labelled with a two-panel, tear-off label and packaged two and two into labelled boxes. The

detachable part of the labels on the bottles will be inserted into the Source Document Worksheets for Tear-Off Labels, which will be retained in the Investigators Study File (ISF).

The boxes will be labelled with a single panel label.

The labelling of the rescue medication, in addition to the distribution of the investigational product and rescue medication, will be carried out by the third party vendor.

3.4.5 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product pack label.

3.4.6 Accountability

The investigational products provided for this study are for use only as directed in this protocol. The investigator or delegate is responsible for drug accountability, and all investigational products supplied should be accounted for at appropriate study visits. The investigator should record the number of capsules given to each patient at visit 2 and visit 4 and should also record the number of returned capsules at visit 4 and visit 5 in the appropriate section of the eCRF. Patients must also bring their rescue medication (GELUSIL® antacid/anti-gas tablets) to each study visit for drug accountability at visit 2, visit 4, visit 5 and visit 6. The unused tablets of GELUSIL® antacid/anti-gas tablets are to be re-dispensed to patients at visit 2 and visit 4, along with a second carton, which will be dispensed at visit 4. The monitor is responsible for sending the remaining investigational product and rescue medication for destruction, which is done according to local requirements.

3.5 Method of assigning patients to treatment groups

The randomisation schedule will be generated and provided by Randcode Support, AstraZeneca R&D Mölndal, using the global randomization (GRand) system.

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as patients are eligible for randomisation. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

The investigational products will be presented as identical capsules. All investigational products will be packed and labelled identically to maintain blinding.

3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists at the study site.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.7 Pre-study, concomitant and post-study treatment(s)

To be eligible for the study patients must have been treated for at least 4 weeks with an optimised unchanged PPI treatment in accordance with the FDA approved label for GERD and GERD related indications. For patients with a history of recently diagnosed reflux (erosive) esophagitis the total time with continuous PPI treatment before enrolment must be at least 8 weeks (with an optimised PPI treatment with doses in accordance with local labelling during the last 4 weeks). The PPI treatment is considered to be optimised when, according to the investigators judgement, no further symptom improvement is to be expected by changing brand or dosing of the PPI. The patient should not change their PPI treatment during the study **and should also avoid changes** of other medications.

Patients should not receive eradication therapy for Helicobacter pylori during the study.

Women of childbearing potential must have started to use one of the highly effective contraceptive methods listed in section 3.3.2 for at least 3 months before enrolment and continue to use the same method strictly as prescribed throughout the study.

The following concomitant medications should not be used during the study:

- Drugs that may interfere with the pharmacodynamic effect of the Investigational Product (eg, Baclofen)
- Drugs that may influence gastrointestinal symptoms
  - PPI (except the PPI that was optimized prior to study enrolment and will be taken during the study, neither the dose or brand of PPI should be changed during the study)
  - Antacids (other than rescue medication [GELUSIL® antacid/anti-gas tablets] supplied in the study)
  - H_2 receptor antagonists
  - Sucralfate
  - Alginates

- Tegaserod
- Domperidone
- Metoclopramide
- Erythromycin
- Drugs with significant anticholinergic effect (eg anticholinergics used in gastro-intestinal disorders; anticholinergics used for Parkinson's disease; anticholinergics used for urine bladder disorders; tricyclic antidepressants)
- Non-steroid anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors (with the exception of occasional use up to 1 day/week)
- Acetylsalicylic acid (ASA) >162 mg
- Biphosphonates
- Antineoplastic drugs

- Drugs that may prolong the QT interval (see Appendix N)
- Drugs that have a narrow therapeutic window (eg warfarin, digoxin, phenytoin, carbamazepine)

Other medications, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the (eCRF).

At the discretion of the investigator, after the completion of the study, patients should be treated according to standard clinical practice.

3.8 Treatment compliance

Authorised personnel will dispense investigational products to the patients at the study site. The patients will be instructed to return all unused investigational products and all packaging materials at visit 4 and visit 5. Returned capsules will be counted and documented in the appropriate section of the eCRF. Study compliance will be assessed by reviewing drug accountability records and will be recorded in the study source documents.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Screening and demographic measurements

The modified RDQ screening instrument (see section 4.2.1 and Appendix C) will be used to screen patients for inclusion into Part 1.

As a part of the screening process at visit 1, patients will complete the modified RDQ screening instrument, which assesses the frequency and intensity of upper gastrointestinal symptoms experienced by the patient over the past 7 days, using the site-based electronic device. This should be done prior to any clinical assessment at the visit, after obtaining informed consent, in order to minimize bias.

To be eligible for inclusion in Part 1 of the study, the patients must have reported in the modified RDQ screening instrument (7 day recall) a burning feeling behind the breastbone with a frequency of at least 3 days over the past 7 days and with at least mild intensity and/or unpleasant movement of material upwards from the stomach with a frequency of at least 3 days over the past 7 days and with at least mild intensity.

After the patient has completed the modified RDQ screening instrument, eligibility will be determined automatically by an algorithm which is programmed in the site-based electronic device. Site staff will be able to view eligibility results (ie, whether the patient meets the above enrolment criteria) and scores on the screen of the site-based electronic device.

If the patient fulfils the RDQ inclusion criteria, additional PRO instruments, as described in the study plan (Table 1) and specified in Table 3, will be completed by the patient using the site-based electronic device.

The following data will be collected and recorded in the eCRF at visit 1:

- Date of informed consent
- Date of birth, sex, race and ethnic group
- History of gastrointestinal disease
- Irritable Bowel Syndrome ROME II and III criteria
- Medical and surgical history
- History of paresthesiae
- History of PPI treatment
- ECG

- Height and weight (BMI)
- BP and pulse
- Nicotine use
- Physical examination
- Laboratory assessments
- Urine pregnancy test (women of childbearing potential)
- Eligibility criteria at enrolment (visit 1)
- Medication on entry into the study
- Dispensed date of rescue medication
- SAE(s) if occurring

4.2 Patient-Reported Outcomes (PROs)

The measurement approach of PROs will focus on establishing the validity, reliability, and ability to detect change (responsiveness) and establish clinically meaningful change of the modified RDQ e-diary in the target patient population. In addition, a responder definition will be established. The validity and reliability of a disease specific measure of the impact of GERD symptoms (modified QOLRAD) in the target patient population will also be assessed.

Several PRO instruments will be used as references when establishing the validity, reliability, and ability to detect change (responsiveness) and clinically meaningful change of the modified RDQ e-diary (GSRS, section 4.2.3, SF-36 v2 acute, section 4.2.4, modified QOLRAD, section 4.2.5, OTE, section 4.2.9). When establishing the responder definition of the modified RDQ e-diary, the TSQ-G, section 4.2.8, and sufficient symptom control question, section 4.2.10, will be used as references. When determining which symptoms in the modified RDQ e-diary are most relevant for the target patient population, the "Most troublesome symptoms" items, section 4.2.2, will be used as a reference.

To determine the validity and reliability of the modified QOLRAD the following instruments will be used: GSRS, section 4.2.3, SF-36 v2 acute, section 4.2.4, the MOS Sleep Scale, section 4.2.7, OTE, section 4.2.9, HADS, section 4.2.11.

HADS, section 4.2.11 will also be used for descriptive purposes.

All PRO instruments will be completed by patients using hand-held electronic devices (see section 4.2.13).

4.2.1 Modified Reflux Disease Questionnaire (RDQ)

The validity, reliability and ability to detect change (responsiveness) of the modified RDQ e-diary will be assessed in this study. In addition, the clinically meaningful change and subsequently a responder definition will be established. Further, the modified RDQ e-diary will be used to determine eligibility for inclusion into part 2 of the study.

The modified RDQ screening instrument (7-day recall) will be used to determine eligibility for inclusion into Part 1, and for comparison with the modified RDQ e-diary recordings from the last 7 days of Part 1.

4.2.1.1 Methods of assessment

Patients will be asked to complete the modified RDQ screening instrument (7-day recall) in an electronic format at visit 1, as described in section 4.1, and at visit 2, and in case of early discontinuation before randomisation.

To measure patient-reported symptoms during Part 1 and during the treatment period (Part 2), patients will be asked to complete the modified RDQ e-diary twice daily, upon waking up in the morning and just prior to bedtime in the evening, starting in the evening on the day of visit 1 and ending in the morning on the day of visit 5.

The RDQ is a brief, self-administered questionnaire designed to evaluate the frequency and severity of heartburn, acid regurgitation and dyspeptic complaints (Shaw et al 2001). During the development process, content validity of the RDQ was informed by literature review, expert opinion, and cognitive debriefing of patients, and the RDQ was updated according to the outcome of cognitive debriefing (Shaw et al 2001). The validity, reliability and responsiveness to change have been assessed in the initial validation study of the RDQ (Shaw et al 2001) as well as in a study of the German version of the RDQ (Nocon et al 2005). In these studies, the items are combined into 4 dimensions (heartburn: burning feeling and pain behind breastbone, dyspepsia: burning feeling and pain in centre of upper stomach, regurgitation: acid taste in mouth and unpleasant movement of material upwards from the stomach, and GERD: terms of heartburn and regurgitation dimensions), where dimension scores are obtained from the arithmetic mean of their item scores.

The RDQ addresses the frequency and intensity of the following symptoms:

- A burning feeling behind the breastbone
- Pain behind the breastbone
- A burning feeling in the centre of the upper stomach
- A pain in the centre of the upper stomach
- An acid taste in the mouth

- Unpleasant movement of material upwards from the stomach

In this study, additional symptom items based on results from cognitive interviews and focus groups in patients with GERD symptoms despite PPI treatment (Report from Mapi Values) and supplemented by clinical experts and literature review, have been added to the RDQ items, thereby comprising the modified RDQ e-diary:

- Burping (gas coming from the stomach through the mouth)
- Hoarseness
- Cough
- Difficulty swallowing
- A bitter taste in your mouth
- Stomach contents (liquid or food) moving upwards to your throat or mouth
- Heartburn

In the modified RDQ screening instrument, the frequency of symptoms over the past 7 days are rated by the patients using a six-graded Likert scale (Did not have; 1 day; 2 days; 3-4 days; 5-6 days; Daily). Similarly, the intensity is rated by the patients using a six-graded Likert scale (Did not have; Very mild; Mild; Moderate; Moderately severe; Severe).

The modified RDQ e-diary will use the same response format for intensity as the modified RDQ screening instrument. The wording of the modified RDQ used at screening and the modified RDQ e-diary can be found in Appendices C and D, respectively.

An RDQ e-diary was used in study D9120C00011, together with a labelled torso. The relevance, content and face validity of the screening and e-diary versions of the RDQ was confirmed in a cognitive debriefing study performed in 80 patients with GERD symptoms despite PPI treatment in the US, France and Japan (Report from Mapi Values). The recommended changes based on the cognitive debriefing study are minor and not believed to influence patients' responses to the questions. However, as additional items were added to the RDQ, further cognitive debriefing of the modified RDQ e-diary will be performed in Part 1, to confirm the content validity of the instrument.

The modified RDQ screening instrument and the modified RDQ e-diary will be used together with a labelled torso, see Appendix E, based on direct feedback from patients in cognitive interviews (Report from UBC, Report from Mapi Values).

4.2.1.2 Derivation or calculation of variables

The e-diary ratings of the 6-graded Likert scale are transformed to numerical values, from "Did not have" = 0 to "Severe" = 5.

A day consists of the recordings performed in the evening and in the following morning. The symptom intensity for a day will be defined as the maximum of the two recordings. Further details on the derivation or calculation of variables are given in section 6.

4.2.2 "Most troublesome symptoms"

The assessment of the "most troublesome symptoms" will be used in the analyses of Part 1, as a reference to determine which symptoms in the modified RDQ e-diary are relevant for the target patient population.

4.2.2.1 Methods of assessment

Patients will be asked to answer the following questions regarding their most troublesome symptoms at both visit 1 and visit 2.

"Which is your most troublesome symptom?"

"Which is your second most troublesome symptom?"

The item pool for troublesome symptoms will be comprised of the symptoms in the modified RDQ screening instrument.

Patients will be able to select only one item as a response to each of the above two questions, but patients will not be able to select the same item twice.

4.2.3 Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS will be used as a reference for the assessment of construct validity of the modified RDQ e-diary and the modified QOLRAD, and to describe the study population.

4.2.3.1 Methods of assessment

Patients will be asked to complete the GSRS (Appendix F) in an electronic format at visit 1, visit 2, 4 and 5, and in the case of early discontinuation.

The GSRS was developed by Dimenäs, Svedlund and Wiklund to evaluate common symptoms of gastrointestinal disorders. On the basis of clinical experience and reports in the literature on gastrointestinal symptoms of patients with Irritable Bowel Syndrome (IBS) and Peptic Ulcer Disease (PUD), a selection of relevant items was made. The original questionnaire is an interview-based instrument (Svedlund et al 1988), but has been modified to become a self-administered questionnaire (Dimenäs et al 1995, Dimenäs et al 1996).

The questionnaire was originally developed in Swedish and has been validated in numerous languages. The GSRS has demonstrated good internal consistency and reliability. On the original European population (1526 patients suspected of duodenal ulcers), Cronbach's alpha of the self-administered version ranged from 0.60 to 0.84 for the individual scales, the lowest reliability being observed for the Abdominal Pain Syndrome scale (Dimenäs et al 1995). Similar values were obtained from a US patient population with GERD (Revicki et al 1998).

Additionally, the GSRS is fairly stable over time and has exhibited good responsiveness to change (Dimenäs et al 1995, Svedlund et al 1988, Revicki et al 1998, Talley et al 2001).

The questionnaire contains 15 items. The degree of discomfort is rated by the patient on a 7-graded Likert scale from "No discomfort at all" to "Very severe discomfort". A mean value for the items in each dimension was calculated (Dimenäs et al 1995, Dimenäs et al 1996). Dimensions and their corresponding items (and item numbers) are presented below:

- Reflux syndrome: (2) heartburn; (3) acid regurgitation
- Abdominal pain syndrome: (1) abdominal pain; (4) sucking sensations; (5) nausea and vomiting
- Indigestion syndrome: (6) borborygmus; (7) abdominal distension; (8) eructation; (9) increased flatus
- Diarrhoea syndrome: (11) increased passage of stools; (12) loose stools; (14) urgent need for defecation
- Constipation syndrome: (10) decreased passage of stools; (13) hard stools; (15) feeling of incomplete evacuation

4.2.3.2 Derivation or calculation of variables

The ratings of the 7-graded Likert scale are transformed to a continuous variable, from "No discomfort at all" = 1 to "Very severe discomfort" = 7.

For each patient and study visit, the score for a dimension is derived as the mean of the separate item scores. If a respondent did not answer at least 50 % of the items in a dimension, the score for that dimension should be set to missing (Halling et al 1999).

4.2.4 The 36-item Short Form Health Survey (SF-36v2 acute)

The SF-36v2 acute will be used as a reference when assessing the construct validity of the modified QOLRAD, and as one of the reference instruments to assess the clinically meaningful change of the modified RDQ e-diary, and when determining the responder definition in the target patient population.

4.2.4.1 Method of assessment

Patients will be asked to complete the SF-36v2 acute (Appendix G) in an electronic format at visit 2 and visit 5 and in the case of early discontinuation.

The SF-36 and the SF-36v2 consists of 36 items combined into eight scales that aggregate 2-10 items each, and two aggregated summary measures (a mental component summary (MCS)) and a physical summary component (PCS)) (Ware et al 1992, Ware et al 2007).

The eight scales are physical functioning (items 3a-3j), role-physical (role limitations caused by physical health problems, items 4a-4d), bodily pain (items 7 and 8), general health (items 1, and 11a-11d), vitality (items 9a, 9e, 9g, and 9i), role-emotional (role limitations caused by emotional problems, items 5a-5c), social functioning (items 6 and 10), and mental health (items 9b, 9c, 9d, 9f, and 9h) (Ware et al 2007). All but one of the 36 items (self-reported health transition) are used to score the eight SF-36 scales. Each item is used in scoring only one scale.

The SF-36 has been administered in general population surveys in the US and other countries (Ware et al 1995) as well as to young and old patients with specific diseases (Ware et al 1993, 2000) and has also been used in GERD (Kulig et al 2003). Relative to the SF-36, the SF-36v2 has improved instructions, item wording, and response categories, improvement in the format recommended by the developers, and more current US population norms (Ware et al 2007)**.** The acute version of SF-36 (Appendix G) has a recall period of one week.

4.2.4.2 Derivation or calculation of variables

The eight scales of the SF-36v2 acute includes items as described previously. The items use Likert scales with 3-6 points. Some of the items are recoded and the scales are derived according to the scoring procedures in the user's manual for the SF-36v2 (Ware et al 2007). All scales are scored positively so that a higher score indicates better functioning, less pain, etc. The aggregated summary scale PCS, contains physical functioning, role-physical, bodily pain, general health, and the MCS contains vitality, social functioning, role-emotional, mental health, respectively.

Raw scores for the scales are computed by summing across items in the same scale and the raw scores are then transformed to a 0-100 scale. This means that each of the 8 scales have a highest possible transformed score of 100, although the highest possible raw score varies.

4.2.5 The modified Quality of Life in Reflux And Dyspepsia (QOLRAD) questionnaire

The validity and reliability of the modified QOLRAD will be assessed in this study. In addition, specific impact dimensions (e.g. sleep and food/drink) will be used as reference when establishing the clinically meaningful change of the modified RDQ e-diary.

4.2.5.1 Method of assessment

Patients will be asked to complete the modified QOLRAD (Appendix H) in an electronic format at visits 1, 2, 4 and 5 and in the case of early discontinuation.

The modified QOLRAD is a self-administered, disease-specific PRO instrument specifically developed to monitor changes in the impact of upper gastrointestinal symptoms on patients' daily lives (Wiklund et al 1998). The QOLRAD was developed in two versions, one for heartburn and one for dyspepsia. Based on a review of the literature, and a review of available and published Health Related Quality of Life questionnaires targeted towards patients with gastrointestinal symptoms a wide range of items was extracted. Data analysis of several

thousand patients with GERD and dyspepsia included in clinical trials completing the Psychological General Well-Being (PGWB) index yielded another set of valid items with confirmed ability to discriminate between items responsive to treatment-induced changes. Finally, a clinician evaluation of clinical relevance of the items selected according to the principles described previously was performed. After these procedures a draft questionnaire was developed. After focus group interviews of patients with a diagnosis of GERD or dyspepsia, performed in Canada and the US, items were added to the initial questionnaire (Wiklund et al 1998).

The QOLRAD consists of 25 items addressing concerns associated with gastrointestinal symptoms, combined into five dimensions:

- Emotional distress (items 12, 14, 15, 17, 19, 22)
- Sleep disturbance (items 8, 10, 11, 18, 21)
- Food/drink problems (items 3, 5, 9, 13, 16, 20)
- Physical/social functioning (items 2, 6, 23, 24, 25)
- Vitality (items 1, 4, 7)

Items are rated on a 7-graded Likert scale. Subscale scores are obtained by summing all item responses and dividing by the number of items (Wiklund et al 1998).

In the initial validation study of QOLRAD, in patients with upper GI symptoms referred for endoscopy, the internal consistency reliability of the subscale scores and the total score were high (Cronbach's alpha ranging from 0.89 to 0.97), and the QOLRAD demonstrated good construct, convergent, and discriminant validity (Wiklund et al 1998). Since then, the QOLRAD has been extensively documented in international and local studies in GERD populations, eg with respect to reliability, validity (Talley et al 2001, Kulich et al 2003), confirmation of the factor structure (Kulich et al 2003), responsiveness (Talley et al 2001), and to assess the impact of GERD (El-Dika et al 2005, Kulig et al 2003).

In the QOLRAD heartburn version, all questions are related to "heartburn or acid regurgitation", with symptoms of heartburn defined as "a burning feeling rising from your stomach or lower chest up towards your neck" and acid regurgitation defined as "acid tasting liquid returning to your throat or mouth". In the modified QOLRAD (Appendix H), to be used in an electronic format in this study, all questions are instead related to "heartburn or regurgitation". Further, instead of defining those symptoms, the instructions state that "HEARTBURN" can be experienced as a burning feeling behind your breastbone" and "REGURGITATION" can be experienced as unpleasant movement of material upwards from the stomach, an acid or bitter taste in your mouth, or stomach contents moving upwards to your throat or mouth.

4.2.5.2 Derivation or calculation of variables

For the QOLRAD as well as the modified QOLRAD, each question is scored from 1 to 7. The lower the score, the higher is the impact severity on patients' daily lives. The dimensions are calculated by deriving a mean value for all items in each dimension.

4.2.6 Impact of Symptoms e-diary items

In order to evaluate alternative diary based PRO instruments for the assessment of the impact of GERD symptoms in the target patient population, the e-diary will include a set of "Impact of Symptoms e-diary items".

4.2.6.1 Method of assessment

To measure the impact of GERD symptoms during Part 1 and during the treatment period (Part 2), patients will be asked to complete impact items in the e-diary twice daily, upon waking up in the morning and just prior to bedtime in the evening, starting in the evening on the day of visit 1 and ending in the morning on the day of visit 5. These items include questions on and related to areas of the impact of GERD symptoms (ie "heartburn or regurgitation") on patients daily lives' reflected in the QOLRAD (section 4.2.5.1). These specific items for the diary version of the impact of GERD symptoms were derived based upon real-time diary questionnaires in the relevant areas of impact, including eating, drinking, and sleeping (Shiffman et al 2006, Roth et al 2005).

The impact items included in the e-diary can be found in Appendix I.

4.2.7 Medical Outcomes Study (MOS) Sleep Scale

The MOS Sleep Scale will be used as a reference when assessing the construct validity of the modified QOLRAD.

4.2.7.1 Method of assessment

Patients will be asked to complete the MOS Sleep Scale in an electronic format at visits 1, 2, 4 and 5 and in the case of early discontinuation.

The MOS Sleep Scale is one subscale of the Medical Outcomes Study (MOS) health status measure. It measures specific aspects of sleep in patients who may have varying co-morbidities, and is hence appropriate for a medically diverse patient population (Hays et al 1992).

The instrument consists of 12 items which can be divided into six subscales: Sleep disturbance (including initiation and maintenance: items 1, 3, 7, and 8), Snoring (item 10), Sleep short of breath or headache (item 5), Sleep adequacy (items 4 and 12), and Somnolence (items 6, 9, and 11). In addition, two summary scores can be calculated, the Sleep Problems Index I (items 4, 5, 7, 8, 9, and 12) and Sleep Problem Index II (items 1, 3, 4, 5, 6, 7, 8, 9 and 12). In addition, sleep quantity can be calculated from item 2, and Optimal sleep can be dichotomized, as described in the scoring manual for the instrument (Spritzer and Hays 2003).

In the original version of MOS Sleep Scale (Appendix J) a time recall period of 4 weeks is used. However, in this study, sleep during the past week will be assessed.

Of the two summary scores, only the Sleep Problems Index II will be calculated as this index is the more comprehensive of the two and, includes more items than Sleep Problems Index I.

4.2.7.2 Derivation or calculation of variables

Items (with the exception of item 2) are transformed to a 0 to 100 metric. Scale scores are then derived by averaging non-missing item responses. A detailed description of how to calculate scores is found in the scoring manual for the instrument (Spritzer and Hays 2003).

4.2.8 Treatment Satisfaction Questionnaire-GERD (TSQ-G)

The TSQ-G will be used as a reference instrument for determining the responder definition in the target patient population.

4.2.8.1 Methods of assessment

The TSQ-G is a disease-specific instrument consisting of 28 items in the 7 domains of 'Symptoms' (items 1, 5, 9, 12, 15, 18, 23), 'Satisfaction' (items 2, 7, 13, 16, 19, 24, 26), 'PRN' (items 3, 17, 21, 25), 'Expectations' (items 10, 22), 'Cost' (items 6, 8, 20), 'Medical Doctor' (items 4, 14, 28), and 'Bother' (items 11, 27) (Coyne et al 2003).

Patients will be asked to complete all 28 items of the TSQ-G at visit 1. At visit 2, visit 4 and visit 5, and in the case of early discontinuation, the 14 items in the 'symptoms' and 'satisfaction' domains will only be completed.

The "symptoms" and "satisfaction" domains will be used to assess changes in satisfaction.

Further, the "symptoms" and "satisfaction" domains, as well as items within these domains, will be related to various responder definitions, to assess to what degree the different variables mirrors patients' satisfaction with treatment.

The symptom descriptors in the TSQ-G have been modified based on patient input in cognitive interviews and focus groups in patients with GERD symptoms despite PPI treatment (Report from Mapi Values). Therefore, regurgitation is mentioned in the instructions as an additional symptom to heartburn, in this TSQ-G version (Appendix K), which will be used in an electronic format in this study.

4.2.8.2 Derivation or calculation of variables

To score the TSQ-G, all items (except items 11, 13, 20, 25, and 27) need to be reverse coded so that high values will reflect a high level of satisfaction and low values will reflect low satisfaction. The current coding with the anchors being 1 = "very strongly agree" and 6 = "very strongly disagree". Consequently positively worded items need to be recoded so that the anchors are 1 = "very strongly disagree" and 6 = "very strongly agree". Negatively worded items (items 11, 13, 20, 25, and 27) should not be reverse coded.

Each subscale as denoted in the previous section should be scored by obtaining the mean item score (range 1-6) within each subscale.

4.2.9 Overall Treatment Evaluation (OTE)

The OTE will be used to identify clusters of patients with various magnitude of symptom change. This allows for the assessment of the modified RDQ e-diary's ability to detect change (responsiveness) and subsequently to establish the clinically meaningful change. The OTE will also be used to identify patients in a stable condition for the test-retest reliability analysis of the modified RDQ e-diary and the modified QOLRAD.

4.2.9.1 Method of assessment

Patients will be asked to complete a study specific version of the OTE in an electronic format at visit 2 (randomisation), visit 4, visit 5, and in the case of early discontinuation.

The wording of the OTE to be used in this study can be found in Appendix L.

The OTE questionnaire has been developed from similar questionnaires, that has been used to determine the minimal important difference (MID) or minimal important change (MIC) in scores of various PRO instruments (Juniper et al 1994, Jaeschke et al 1989).

4.2.9.2 Derivation or calculation of variables

The OTE questionnaire uses a 15-graded scale, where 7 = a very great deal better, 0 = about the same and –7 = a very great deal worse.

Patients with OTE scores of 0,1 and -1 will be classified as "unchanged" and "in a stable condition". Patients with OTE scores of 2, 3, 4, 5, 6 or 7 will be classified as "improved", and patients with OTE scores of -2, -3, -4, -5, -6 or -7 will be classified as "deteriorated". Further, patients with OTE scores of 2 and 3 will be classified as having experienced a "small improvement", patients with OTE scores of 4 and 5 will be classified as having experienced a "moderate improvement" and patients with OTE scores of 6 and 7 as having experienced a "large improvement". Further, patients with OTE scores of -2 and -3 will be classified as having experienced a "small deterioration", patients with OTE scores of -4 and -5 will be classified as having experienced a "moderate deterioration", and patients with OTE scores of -6 and -7 will be classified as having experienced a "large deterioration".

4.2.10 Sufficient Symptom Control

The question addressing sufficient symptom control will be used as a reference when determining the responder definition in the target patient population.

4.2.10.1 Methods of assessment

Patients will be asked to complete the following question regarding their self-reported perceived symptom control at visit 1, visit 2, visit 4, 5, and in the case of early discontinuation:

At visits 1 and 2: "Does your current medication give sufficient control of your symptoms"?

At visit 4 and 5: "Does the study medication give sufficient control of your symptoms"?

Response categories: "Yes" or "No".

The question to be used at visits 4 and 5 has previously been used in an omeprazole study (Junghard et al 2003) and the previous AZD3355 study, D9120C00011.

Patients' responses to this question will be related to the various responder definitions. This will allow the assessment of the proportion of patients who report "sufficient symptom control" for each responder definition level.

4.2.10.2 Derivation or calculation of variables

Frequency and proportion of patients in each of the symptom control categories ("Yes" or "No") will be calculated.

4.2.11 Hospital Anxiety and Depression Scale (HADS)

The HADS will be used to describe the study population, and is one of the instruments to be used to assess the construct validity of the modified QOLRAD.

4.2.11.1 Method of assessment

Patients will be asked to complete the HADS in an electronic format at visit 1 only.

The HADS is a measure of aspects of patients' psychological state specifically anxiety and depression (Snaith et al 1994).

The HADS (Appendix M) consists of 14 items measuring the level of anxiety (7 items) and depression (7 items) in the past week. Each item has 4 response categories, reflecting a continuum of increasing level of anxiety or depression.

Scale scores range from 0 (no symptoms) to 21 (maximum distress) for both the depression and anxiety subscales. For each construct, a score below 8 is in the normal range, 8-10 is mild, 11-14 is moderate, and 15-21 indicates a severe disorder of the relevant mood. The validity and reliability of the HADS have been reported in several studies (Herrmann 1997), but not in this study population.

4.2.11.2 Derivation or calculation of variables

The Depression (D) and Anxiety (A) subscale scores are calculated by adding the scores for items in the respective subscale, as described in the HADS manual (Snaith et al 1994). No total score for the HADS is calculated.

4.2.12 Recordings of use of rescue medication

4.2.12.1 Method of assessment

Patients will be asked to report their use of rescue medication in the e-diary twice daily, upon waking up in the morning and just prior to bedtime in the evening, starting in the evening on the day of visit 1 and ending in the morning on the day of visit 5.

They will be asked the following questions in the evening:

"Have you taken any GELUSIL® antacid/anti-gas tablets since waking today?"

Response categories: "Yes" or "No".

Only if yes: "How many GELUSIL® did you take since waking today?"

In the morning, the questions will have the following wording:

"Have you taken any GELUSIL® antacid/anti-gas tablets during the nighttime?"

Response categories: "Yes" or "No".

Only if yes: "How many GELUSIL® did you take during the nighttime?"

4.2.12.2 Derivation and calculation of variable

Number of GELUSIL® antacid/anti-gas tablets used during each day will be calculated.

4.2.13 Administration of PRO instruments

The PRO instruments are be self-administered and the patients will be asked to complete the PRO questionnaires and questions in electronic format using hand-held electronic devices. When completing PRO instruments at visits, patients will use a site-based electronic device. For the twice daily registrations of the modified RDQ e-diary and the Impact of Symptoms e-diary items, patients will use a home-based electronic device (e-diary device). The site-based and home-based devices will be of the same type.

At study visits, the PRO questionnaires and questions will be completed as described in Table 3 and will automatically appear on the screen of the site-based electronic device, when the site staff selects the appropriate visit in the device.

The PRO questionnaires and questions for the twice daily e-diary recordings will be automatically appear on the screen of the e-diary device in the order listed in Table 4, when the patient activates the bedtime and morning reports, respectively. Patient will be asked to complete the bedtime report just prior to bedtime in the evening, and the morning report upon waking up in the morning. The bedtime report will be available daily from 8:00 pm until 2:00 am the next day, for completion by the patient. There will be a reminder alarm at 11:00 pm if the subject has not yet completed the bedtime report at that time. The morning report will be available daily from 05:00 am until 11:00 am, for completion by the patient. The patient will

be asked to set a flexible wakeup alarm after completion of the bedtime report, to be used as a reminder for the completion of the morning report.

Standard procedures for minimising bias and enhancing ePRO compliance will be followed throughout the study.

The patients will be instructed to complete all questionnaires and questions independently, at study visits as well as when completing the e-diary questions, so that the responses reflected the patient's own perception. Each site will have a designated quiet space for patients to use when completing the PRO instruments at the study visits.

Dedicated study staff at each site will be responsible for ensuring that the ePRO process will be followed according to the specific instructions from the clinical study team and the ePRO provider. A detailed manual, which covers the description of the ePRO solution and practical issues that may arise, will be provided to the study staff.

Before completing the modified RDQ screening instrument, the patient will receive training in how to use the site-based electronic device. If eligible for inclusion into Part 1 of the study, the patient will receive extended training on how to use the e-diary device and how to transfer the data. There will also be specific instructions for the respective PRO instruments in the electronic devices.

Patients will be instructed to start recording in the e-diaries in the evening on the day of visit 1, with last recording in the morning on the day of visit 5. During the training the importance of the twice-daily e-diary recordings upon waking up in the morning (reporting night-time symptoms) and just prior to bedtime in the evening (reporting day-time symptoms) will be emphasised.

The site staff will transfer the data from the site-based electronic device via a wireless or analogue modem, depending on feasibility, to a centralised database, as soon as possible after completion of the PRO instruments at the study visit. Similarly, the patient will transfer their e-diary data via a wireless or analogue modem to a centralised database. To carry out the data transfer, the patient needs to place the e-diary device on the modem each night for automatic transfer of the data. Once transferred, the data will be accessible in a secure fashion on a Web site that is available to the specific study site. In addition, the data will be accessible to the study monitor and the AstraZeneca clinical study team. If a data transfer cannot be completed from the patient's home, it may be done from work or another suitable location. If none of the previous means can be used, then the data transfer can be done at the regularly scheduled study visits.

The study staff will be required to monitor that the patients have completed the appropriate PRO instruments at each visit. Further, the study staff will be required to monitor the patients' compliance with the twice daily recordings in the e-diary on a daily basis using the Web site. If the compliance is deemed not optimal, the study staff will contact the patient via telephone to assess if the issue is technical or if the patient needs additional instructions or support.

In addition, a check of the e-diary device (battery status and data transfer) and a review of e-diary compliance will be done at visits 2 and 4. A review of e-diary compliance will also be done at visit 3 (phone visit). At visit 5, a check of the e-diary device (data transfer) and a review of e-diary compliance will be performed, and then the e-diary device will be collected.

Table 3 PRO assessments at visits

	Part 1	**Part 2 (treatment period)**			
Visit	**1**	**2**	**3**	**4**	**5**
Visit Description	Enrolment	Randomisation	Phone contact		End of treatment
Visit Window (No. Weeks ± No. Days)	**12 to 8 days prior to randomisation**	**Day 1**	**5 to 9 days after randomisation**	**12 to 16 days after randomisation**	**26 to 30 days after randomisation**
Site-based PRO assessments (using the site-based electronic device)[a]:					
Modified RDQ screening instrument (section 4.2.1)	X	X			
Most troublesome symptom question (section 4.2.2)	X	X			
GSRS (section 4.2.3)	X	X		X	X
TSQ-G (section 4.2.8)	X (28 items)	X (14 items)		X (14 items)	X (14 items)
OTE (section 4.2.9)		X		X	X
Sufficient symptom control question (section 4.2.10)	X	X		X	X
SF-36v2 acute (section 4.2.4)		X			X
Modified OOLRAD (section 4.2.5)	X	X		X	X
MOS Sleep Scale (section 4.2.7)	X	X		X	X
HADS (section 4.2.11)	X				

[a] Patients make those assessments at site visits, using a site-base electronic device. The instruments will appear automatically in the above order when activating a specified visit.

Table 4 PRO assessments using e-diary device

	Part 1	**Part 2 (treatment period)**			
Visit	**1**	**2**	**3**	**4**	**5**
Visit Description	Enrolment	Randomisation	Phone contact		End of treatment
Visit Window (No. Weeks ± No. Days)	**12 to 8 days prior to randomisation**	**Day 1**	**5 to 9 days after randomisation**	**12 to 16 days after randomisation**	**26 to 30 days after randomisation**
Twice daily e-diary recordings (using e-diary device) [b]:					
Modified RDQ e-diary (section 4.2.1)	X [b]--------	----------	---------	----------	X [b]
Impact of symptoms e-diary items (section 4.2.6)	X [b]--------	----------	---------	----------	X [b]
Use of rescue medication (section 4.2.12)	X [b]--------	----------	---------	----------	X [b]

[b] Patients makes twice daily recordings, starting before bedtime in the evening on the day of visit 1 and ending in the morning on the day of visit 5, using an e-diary device. The PRO instruments will appear in the order listed in Table 4.

4.3 Cognitive interviews

4.3.1 Cognitive interviews

The aims of the cognitive interviews are to provide patient-based information in addition to data derived from the PRO instruments to establish the content validity of the symptoms and concepts to be used in the AZD3355 clinical study program, and to provide supplementary information in determining the definition of clinically meaningful change.

Cognitive interviews will be carried out in order to accomplish the following:

- Confirm the relevance of symptoms in the RDQ to patients in the target patient population
- Assess the relevance of the additional symptoms in the modified RDQ to patients in the target patient population
- Gain a deeper understanding of whether and how GERD symptoms are troublesome and which GERD symptoms are the most troublesome in the target patient population
- Assess the relevance of the impact concepts (ie, dimensions) from the modified QOLRAD to patients in the target patient population

- Assess the relevance of additional impact concepts to patients in the target patient population
- Assess whether patients in the target patient population attribute the impact on aspects of their life that they are being asked to rate, to heartburn and regurgitation
- Assess patients' perception of change and magnitude of change, attribution and what is clinically meaningful to them (including if GERD symptoms are no longer troublesome) in the target patient population

Enrolled patients at pre-identified study sites, who consent to participate in the cognitive interviews, will have appointments arranged for mutually acceptable times. Not all patients who consent will be able to participate based on availability of interviewers . The interviews will be face-to-face to further examine patients' experience of GERD symptoms and the impact of symptoms on their lives. The goal is to conduct two interviews each in approximately 40 patients.

The first interview will take place before randomisation in conjunction with visit 2 (the randomisation visit), with a time window of up to 5 days prior to visit 2.

The second interview will take place at the end of Part 2 in conjunction with visit 5 (the end-of-treatment visit), with a time window of 7-days prior to or 2 days after visit 5. Patients who are not able to participate in the second cognitive interview in the prescribed time period or those who discontinue from the study may be replaced with other patients. The interviewers will *not* know the patients' status with respect to treatment group or treatment response.

When an interview is conducted on the day of study visit 2 or 5 , then the interview will be carried out after the completion of the PRO instruments, and prior to clinical assessments.

Trained personnel using cognitive debriefing techniques will perform the interviews. The interviews will be no longer than 60 minutes, but the study site should plan to schedule a 90-minute time period to allow for set-up of the audio recording equipment and to provide some flexibility to sites and/or patients in the event unforeseen scheduling issues arise.

All cognitive debriefing interviews will be audio recorded, with permission obtained through the informed consent process. Patients will be informed that this data will be examined by various personnel at AstraZeneca, including, but not limited to, the study team, as well as representatives of AstraZeneca (eg, the contracted Contract Research Organization [CRO]), the FDA, other Department of Health and Human Services agencies and other government agencies in the United States and in foreign countries. Furthermore, the patients will be informed that this information will be used to assess the experience of patients in this study and that the data will also be used by AstraZeneca to aid in the design of future studies and programs to treat this condition. All data will be confidential and the patient identifiers used will conform to applicable regulations, so as to preserve patient confidentiality (eg, to assure matching between the audio recording and the subsequent transcript). Data from the audio recordings of the interviews will be transcribed to paper and analyzed using a number of

qualitative techniques particular to this methodology (Ericsson et al 1980,Campanelli et al 1991).

Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (ie, not in the clinical study report) and the data (ie, transcriptions) will not be entered into the study database.

4.4 Safety measurements and variables

Table 5 Safety objective and variables

Objective	Variables
To assess the safety and tolerability during 4 weeks treatment with AZD3355 65 mg bid as add-on treatment to a PPI in partial responders to PPI treatment who still experience GERD symptoms	BP, pulse, ECG, physical examination, laboratory variables, AE recording. Data on paresthesiae collected in specific eCRF module. To be used if patients spontaneously report paresthesiae as an AE

The methods for collecting safety data are described below.

4.4.1 Adverse events

4.4.1.1 Definitions

The definitions of AEs, SAEs and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

Adverse event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening

- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigators, who in completing the relevant eCRF must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – investigational product – other medication?". For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Global Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to early discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.4.1.2 Recording of adverse events

AEs will be collected from time of first administration of investigational product until the end of the study. SAEs will be collected from the time informed consent is signed through the entire study period.

AE spontaneously reported by the patient and/or in response to an open question "have you had any health problems during the study since the previous visit" from the study personnel or revealed by observation will be recorded during the study visit at the investigational site and at the follow-up visit.

Findings and values related to physical examinations will be defined as AEs if they are considered clinically relevant deteriorations compared with baseline and pre-dose values, as judged by the investigator.

Deterioration in laboratory values, BP and pulse and ECG need not to be recorded as AEs. However, abnormal values that constitute an SAE, or lead to early discontinuation of administration of any investigational product must be reported and recorded as AEs.

Onset, resolution, maximum intensity, early discontinuation due to AE, action taken, outcome, causality and whether it constitutes an SAE or not will be reported in the eCRF for each AE.

The intensity rating is defined as:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in section 4.4.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Any AEs that are unresolved at the patient's last AE assessment in the study (ie, at the follow-up visit) are to be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in section 9.3, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Should a pregnancy occur, it must be reported in accordance with the procedures described in section 9, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive method.

4.4.1.3 Spontaneously report of paresthesiae

If the patient spontaneously reports paresthesiae (defined as "an abnormal touch sensation in the absence of an external stimulus"), a more thorough questioning will be done, asking for frequency, the patients´ description of the symptoms, start of symptoms in relation to intake of investigational product, duration of symptoms and level of discomfort. All patients reporting paresthesiae will have a neurological examination by the investigator. Patients experiencing daily paresthesiae for at least 7 consecutive days will be withdrawn from intake of investigational product, be referred to a board certified neurologist for examination and

followed-up after 12-16 days by the investigator (visit 6). A copy of the report from the neurologist must be provided to AstraZeneca.

4.4.1.4 Symptoms of the disease under study (DUS)

Some adverse conditions are regarded as part of the natural history of the disease/procedures under study.

The following symptoms will not be recorded as AEs during treatment with investigational product unless they fulfil the criteria for SAEs or lead to early discontinuation of the investigational product, since these symptoms are measured outcome variables of interest in the study:

- A burning feeling behind the breastbone, pain behind the breastbone, a burning feeling in the centre of the upper stomach, a pain in the centre of the upper stomach, an acid taste in the mouth, unpleasant movement of material upwards from the stomach, burping (gas coming from the stomach through the mouth), hoarseness, cough, difficulty swallowing, a bitter taste in the mouth, stomach contents (liquid or food) moving upwards to the throat or mouth and heartburn.

4.4.1.5 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

SAE information will be entered and submitted into the Clinical Operation On Line (COOL) system on the relevant eCRF modules. An automated email alert will be sent to the designated AstraZeneca representative who will work with the investigator to ensure that all the necessary information is available in COOL within the required time frames. The AstraZeneca representative will notify the appropriate AstraZeneca Patient Safety Data Entry Site through COOL via email that a completed electronic SAE module and relevant information from other appropriate eCRF modules is available in COOL. If COOL is unavailable, the investigator should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator is responsible for completing the eCRF as soon as COOL becomes available again.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If follow-up indicates a change in the SAE from serious to fatal or life-threatening, this information needs to be available in COOL within 1 day.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that become serious but which is not fatal or life-threatening a report should be received within 5 days.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Patient Safety Data Entry Site receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

4.4.2 Laboratory safety measurements and variables

4.4.2.1 Methods of assessment

An extended laboratory screen with blood and urine sampling for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the enrolment visit (visit 1) and at the follow-up visit (visit 6). If a patient needs an early discontinuation visit, an extended laboratory screen (including a urine pregnancy test) should be done. If a patient needs an unscheduled visit, an extended laboratory screen (except a urine pregnancy test) could be done.

A laboratory screen with blood and urine sampling for determination of clinical chemistry, haematology and urinalysis parameters will be taken at visit 2, visit 4 and visit 5. The laboratory samples will be analysed at a central laboratory, Quintiles Laboratories (QLABS), Ltd., Smyrna, Georgia, USA, except for the urine pregnancy test, which will be done by dipstick at the study site and entered into the Pregnancy Test (PREG) module of the eCRF. See Table 7 for the total volume of blood that will be drawn from the patients throughout the conduct of the study.

A urine pregnancy test for women of childbearing potential only will be conducted at visit 1, visit 2, visit 6 and early discontinuation visits.

Table 6 Summary of the laboratory safety variables analysed in the study

Clinical chemistry	**Haematology**
S-Aspartate transaminase (AST)	B-Haemoglobin
S-Alanine transaminase (ALT)	B-Red blood cell (RBC) count
S-Alkaline phosphatase	B-White blood cell (WBC) count
S-Total bilirubin	B-Platelet count
S-Creatinine	B-Reticulocyte count
S-Thyroid stimulating hormone (TSH)[a]	B-WBC differential count
S- Free Thyroxine (free T4)[a]	B-Mean corpuscular volume (MCV)
S-Blood urea nitrogen (BUN)/urea	B-Mean corpuscular haemoglobin concentration (MCHC)
S-Albumin	
S-Sodium	**Urinalysis (dipstick)**
S-Potassium	U-Protein
S-Magnesium	U-Glucose
S-Calcium	U-Blood
S-Creatine phosphokinase (CPK)	Urine pregnancy test[b] (dipstick)
P-Non-fasting plasma glucose	
High-sensitivity C-reactive protein (hs-CRP)	
B-Haptoglobin	
Helicobacter Pylori (H pylori), antibody immunoglobuin G [IgG]) test[c]	

[a] Conducted at visit 1, visit 6 and early discontinuation visits.
[b] Conducted at visit 1, visit 2, visit 6 and early discontinuation visits only for women of childbearing potential.
[c] Conducted at visit 1 only.

Laboratory values outside the reference ranges suspected to be of any clinically significance could be re-checked during an unscheduled visit. Randomised patients who develop clinically significant abnormal laboratory values must be followed until normalisation or for as long as the investigator considers necessary.

4.4.2.2 Derivation or calculation of outcome variables

See section 4.4.1.2 for how an AE based on laboratory values will be recorded and reported.

4.4.3 Vital signs, ECG and physical examination

4.4.3.1 Methods of assessment

Physical examination (ie, general appearance, skin, head and neck, lymph nodes, thyroid, muscoskeletal/extremities, cardiovascular, lungs, abdomen and neurology, including cranial nerve functions) will be done at visit 1, visit 2, visit 5 and visit 6. dECG will be recorded at all visits at the study site (at visit 2, prior to and 1 hour after the first dose of investigational product) including at the early discontinuation visit. Supine pulse and BP will be obtained at the study site at visit 1, supine and standing pulse and BP will be obtained at the study site at visit 2, 4, 5 and 6 and at the early discontinuation visit if applicable. At visit 2 the supine and standing pulse and BP will be obtained after the dECG recordings prior to and 1 hour after the first dose of investigational product.

At visit 2, 4, 5 and 6 dECG will be performed after the PRO assessments and cognitive interviews are completed (if applicable).

ECG

eResearch Technology (eRT), Inc. (Philadelphia, Pennsylvania) will provide the equipment and review of dECGs. The dECGs will be acquired utilizing the Mortara ELI 150, a Transtelephonic Modem-Based 12-Lead ECG Delivery.

After the patient has been supine for at least 10 minutes, three standard 12-lead digital ECG recordings (triplicate) will be performed within a 5-minute period while the patient remains supine. Printouts of the dECG (paper speed 25mm/sec) will be obtained for review by the investigator. ECGs will be evaluated as either "Normal" or "Abnormal" with special attention to QTcF and recorded in the eCRF. If an ECG is evaluated as "Abnormal", the specific abnormality and investigator judgement regarding clinical significance is required.

All dECGs will be reviewed by a trained eRT Cardiac Safety Specialist for correct lead and beat selection and caliper. Each dECG will be submitted to a Cardiologist through eRT for clinical evaluation and verification of the caliper placement. A final report from each dECG will be delivered by eRT to the investigator within 72 hours.

At visit 2 the ECG electrodes should remain on the patient to ensure that the same position is used for the dECG recordings before and after the first dose of IP.

Pulse and BP

Supine BP and pulse will be measured in all patients at visit 1 immediately following the dECG recording and before blood samples are obtained.

Supine and standing BP and pulse will be measured in all patients at visit 2, 4, 5, 6 and at the early discontinuation visit immediately following the dECG recordings and before blood samples are obtained.

The following procedure should be applied for each measurement: After the supine BP and pulse have been measured, the patient will be instructed to stand with arms relaxed at their sides. BP and pulse will then be measured after 1 minute in the upright position.

4.5 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 7 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	12.5 mL (extended lab screen)	2 (visits 1 and 6/early discont)	25.0 mL
		9.0 mL	3 (visits 2, 4 and 5)	27.0 mL
	Haematology	3.0 mL (extended lab screen)	2 (visits 1 and 6/early discont)	6.0 mL
		3.0 mL	3 (visits 2, 4 and 5)	9.0 mL
Total				67.0 mL

However, if additional tests are required for the patient's safety ie unscheduled visits, retests etc, the volume of blood might be increased.

4.5.1 Analysis of biological samples

4.5.1.1 Clinical chemistry samples

The analyse stability limits defined by the central laboratory, QLABS, will be applied to all analyses performed on behalf of AstraZeneca. QLABS will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by QLABS may be amended in accordance with its Standard Operating Procedures.

If QLABS chooses to sub-contract the analytical work to another laboratory, QLABS must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported.

5. DATA MANAGEMENT

The patients will use electronic devices for collection of the PRO data (see section 4.3) and trained study personnel at the study site will be responsible for entering the patient identifier data and visit data in the site-based electronic device and e-diary device (see section 8.4). The ePRO system will be provided by invivodata, Pittsburgh, Pennsylvania, USA. The ePRO data will be transferred either via telephone modems or wireless data transfers to a central database.

The ePRO system is a specialised data capture appliance designed for entry of data in a way that is attributable, secure and accurate in compliance with FDA´s Final Rule: Electronic Records; Electronic Signature (21 CRF Part 11).

After the ePRO data have been transferred to the central database, it can be reviewed via a secure access to a web-server. All data will be time stamped and changes on the visit and identifier data will be tracked in the systems audit trail. Each user needs to have system training before any access will be given out. All actions on data are to be accomplished using the system controls compliant with 21 CRF part 11 that are built in to the system application used to collect, clean, review and archive clinical study data.

The clinical data will be entered into COOL, the web based data entry system, at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the COOL system and according to the eCRF Instructions.

The eCRF Instructions will also provide the study site with data entry instructions. Data entered in the COOL system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered reviewed, edited and Source Data Verification (SDV) performed the principal investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A CD/DVD containing a copy of eCRF data will be distributed to the study sites for archiving in the ISF.

All coding will be done in accordance with AstraZeneca standard procedures, and continually throughout the study. Queries can be raised by the coding expert at any time during the study period and the query tool in COOL will be used.

AE, diagnosis from medical history and procedures from surgical history will be classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA, latest version throughout the study). “The Lowest Level Term” that best reflect the term used by the investigator will be chosen when classifying the terms and “Preferred Terms” will be used mainly for output (data presentation) for the grouping of terms. Concomitant medication will be classified according to the AstraZeneca Drug Dictionary (AZDD), the Anatomical Therapeutic Chemical (ATC) system and the Committee for Medicinal Products for Human Use (CHMP) route of administration dictionary.

Laboratory data will be delivered to AstraZeneca R&D Mölndal, Sweden, by the central laboratory. The laboratory data will be loaded into the study database.

A central ECG vendor will be used to collect dECG data. Sites will transmit the dECG data to the vendor's central database using equipment provided by the vendor. The vendor will identify, examine and analyse the data and will send the ECG report to site.

Online study reports will be accessible to the study team during the study. The source files will be returned to AstraZeneca R&R, Mölndal.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) for the analyses involving Part 2 data (ie post randomisation data) will be prepared before unblinding of the data.

The robustness of results with respect to the handling of missing data will be explored.

6.2 Description of analysis sets, Part 1

All enrolled patients with available data will be used in the analyses described below.

6.3 Methods of statistical analysis, Part 1

6.3.1 Calculation of variables, modified RDQ e-diary

In the statistical analysis, the sequences of observations consisting of modified RDQ morning and evening e-diary registrations will be imputed separately according to the following rules. If a single observation is missing, the missing value will be replaced by the larger (more intense) of the two surrounding values. If two or more consecutive observations are missing the values will remain missing. Values for a *day* (24 h period) will then be constructed using the imputed evening and morning registrations. A day will consist of the evening and the following morning registration. Hence, the day denoted in the following sections as the last day prior to visit 2, will consist of the evening before visit 2 and the morning of visit 2. The symptom intensity for a day is defined as the maximum of the two registrations. If either the morning or the evening registration is missing, the corresponding day will be set to missing.

The symptom cluster intensity for a day will be defined as the mean symptom intensity of the items that form the cluster.

When calculating item and symptom cluster scores for a week, either the mean or the maximum value of the daily intensities during the week could be used. In order to decide which definition to use throughout the study, both will be calculated for a symptom cluster consisting of the modified RDQ symptom items a burning feeling behind the breastbone, heartburn, unpleasant movement of material upwards from the stomach, an acid taste in the

mouth, a bitter taste in your mouth and stomach contents (liquid or food) moving upwards to your throat or mouth (ie the modified RDQ items that the modified QOLRAD questionnaire instruction refer to as heartburn or regurgitation), using e-diary registrations the last 7 days prior to visit 2. Those two symptom cluster scores will then be related to the dimension scores of the modified QOLRAD, using responses at visit 2 for the QOLRAD dimensions Emotional distress, Food/drink problems and Sleep disturbance as described in section 4.2.5.1. When relating to Sleep disturbance, only morning e-diary registrations will be used. If one of the definitions for a weekly score clearly reflects the symptom burden more efficiently, that definition will be used in the study. Else the mean intensity over the week will be used.

6.3.2 Symptom clusters based on the modified RDQ e-diary

Exploratory factor analysis will be undertaken in an attempt to study the underlying concepts in the modified RDQ for the morning and evening registrations combined as well as for the morning registrations separately using the following variables for each symptom:

- Number of days with symptom (having symptom defined as symptom intensity greater than “Did not have”) during the last seven days prior to visit 2. If registrations for two or more days are missing during the seven day period for a patient, the number of days with symptom will be set to missing.

- Mean symptom intensity during last seven days prior to visit 2. If registrations for two or more days are missing during the seven day period for a patient, the mean symptom intensity will be set to missing.

- Number of morning registrations with symptom during the last seven mornings prior to visit 2. If two or more morning registrations are missing during the seven day period for a patient, the number of mornings with symptom will be set to missing.

- Mean symptom intensity during last seven morning registrations prior to visit 2. If two or more morning registrations are missing during the seven day period for a patient, the mean symptom intensity will be set to missing.

Principal components factor analyses with varimax and oblimin rotation will be used. All loadings for the retained factors will be presented.

The selection of symptom clusters and corresponding variables to be evaluated in the second part of the study will be based on the evaluation of the exploratory factor analysis together with the other results from the first part of the study.

There are some items in the modified RDQ that are expected to describe the same symptom. The item ‘Heartburn’ is included to serve as a comparison to ‘A burning feeling behind the breastbone’. In the second part of the study, ‘A burning feeling behind the breastbone’ will be the item of choice. Based on the results from the first part of the study, one of the items

'Unpleasant movement of material upwards from the stomach' and 'Stomach contents (liquid or food) moving upwards to your throat or mouth' will be used moving forward.

6.3.3 Factor analysis, modified QOLRAD

Exploratory factor analysis will be undertaken in an attempt to study the underlying concepts in the modified QOLRAD using the item responses at visit 1. Principal components factor analyses with varimax and oblimin rotation will be used. All loadings for the retained factors will be presented.

The factor structure of the modified QOLRAD will be compared to the original QOLRAD heartburn version. If a new factor structure for the modified QOLRAD is a better fit for the study population, this new factor structure will be used moving forward.

6.3.4 Factor analysis, impact of symptoms e-diary items

Exploratory factor analysis will be undertaken in an attempt to study the underlying concepts of the impact e-diary items, using the mean score during the last seven registrations prior to visit 2 for the items that are reported on an 11-graded scale. If two or more registrations are missing during the seven day period for a patient, the mean value will be set to missing. Principal components factor analyses with varimax and oblimin rotation will be used. All loadings for the retained factors will be presented.

6.3.5 Reliability

6.3.5.1 Test retest, modified QOLRAD

Test-retest reliability will be investigated for the modified QOLRAD using Intraclass Correlation Coefficients (ICC). The within-patient and between-patient mean square will be calculated by two-way analysis of variance (ANOVA) with the factors of patient and visit (1 and 2), using subjects in a stable condition between visit 1 and 2. A stable patients is defined as a patient who had "About the same", "Almost the same, hardly worse at all" or "Almost the same, hardly better at all" on OTE at visit 2. The ICC will be calculated for the derived clusters of the modified QOLRAD obtained through the factor analysis described in section 6.3.3. A cluster score will be calculated as the mean value of the items in the cluster. Other ways of calculating cluster scores may be explored. The test-retest reliability intraclass correlation coefficient (R) will be estimated as:

$$\hat{R} = \frac{BMS - WMS}{BMS + (k_0 - 1)WMS}$$

where BMS and WMS are the mean square values between-patients and within-patients respectively, and k_0 denotes the number of replicates per patient (two in this case).

A 95% confidence interval for R will be estimated as

$$R \geq \frac{\frac{BMS}{WMS} - F_{N-1,K-N,\alpha/2}}{\frac{BMS}{WMS} + (2-1)F_{N-1,K-N,\alpha/2}}, \quad R \leq \frac{\frac{BMS}{WMS} - F_{N-1,K-N,1-\alpha/2}}{\frac{BMS}{WMS} + (2-1)F_{N-1,K-N,1-\alpha/2}}$$

where N = number of patients and K = number of measurements.

In order to be included in the test-retest calculations, a patient has to have non-missing cluster scores at both visit 1 and visit 2.

ICC values < 0.4 will be considered to represent poor reliability, values > 0.75 excellent reliability, and values in between fair to good reliability (Fleiss 1986).

Missing values

If a patient answered less than 50% of the items in a cluster, the cluster score will be set to missing.

6.3.5.2 Internal consistency

The consistency of questions within the modified RDQ symptom clusters and modified QOLRAD clusters will be evaluated using Cronbach's alpha coefficient (Cronbach 1951). Cronbach's alpha will be estimated as

$$\alpha_c = \frac{m}{m-1}\left(1 - \frac{\sum Var(x_i)}{Var(\sum x_i)}\right)$$

where m is the number of items in the cluster, $Var(x_i)$ is the estimated variance of the i^{th} item and the summation is over all items within a cluster. Ninety five% confidence intervals for Cronbach's alpha coefficients will be presented. A high alpha coefficient suggests that the items within a cluster measure the same construct. A minimum value of 0.70 has been recommended (Fayers et al 2007).

For the modified RDQ, Cronbach's alpha will be calculated for each multi-item symptom cluster derived through the factor analysis of 24 h period values (see section 6.3.2. Item scores will be defined as the mean or maximum intensity (see section 6.3.1 of the last 7 days prior to visit 2.

For the modified QOLRAD, Cronbach's alpha will be calculated for each multi-item cluster derived through the factor analysis described in section 6.3.3, using the item responses at visit 2.

6.3.6 Construct validity

6.3.6.1 Convergent and discriminant validity

The correlation between symptom clusters in the modified RDQ and modified QOLRAD and dimensions in other instruments will be investigated using Spearman's rho. 'Convergent' refers to the idea that high correlations are expected between those dimensions that are theoretically related and 'discriminant' to the idea that low correlations are expected between those dimensions that are theoretically unrelated.

For the modified RDQ, symptom clusters derived through the factor analysis of 24 h period values (see section 6.3.2) will be used. Symptom cluster scores will be defined as the mean or maximum (see section 6.3.1) daily symptom cluster intensity of the last 7 days prior to visit 2.

For the modified QOLRAD, the derived clusters as described in section 6.3.3 will be used. The responses (visit 1 or visit 2) used will vary depending on the availability of the reference instruments (see below).

The following instruments will be used to evaluate convergent and discriminant validity of the modified RDQ and modified QOLRAD:

- Modified RDQ vs GSRS: GSRS dimension scores will be based on responses at visit 2.
- Modified QOLRAD vs GSRS: Modified QOLRAD and GSRS dimension scores will be based on responses at visit 1 as well as visit 2.
- Modified QOLRAD vs SF-36v2 acute: Modified QOLRAD and SF-36v2 acute dimension scores will be based on responses at visit 2. The eight SF-36v2 acute dimensions and two summary dimensions described in section 4.2.4.1 will be used.
- Modified QOLRAD vs MOS sleep scale: Modified QOLRAD and MOS sleep scale dimension scores will be based on responses at visit 1 as well as visit 2.
- Modified QOLRAD vs HADS: Modified QOLRAD and HADS dimension scores will be based on responses at visit 1.

The correlation coefficients (Spearman's rho) will be presented.

Missing values

If a patient answered less than 50% of the items in a dimension, the dimension score will be set to missing.

6.3.6.2 Known groups validity

The GSRS reflux syndrome dimension scores (see section 4.2.3) from visit 2 will be used to separate patients into three groups that can be expected to score differently in questions regarding heartburn and acid regurgitation in other instruments. The cut-off for the separation

will be based on previous data. The mean cluster score of the modified RDQ symptom clusters and modified QOLRAD clusters will be presented graphically by GSRS group.

For the modified RDQ, the derived symptom clusters of 24 h period values (see section 6.3.2) will be used. Symptom cluster scores will be defined as the mean or maximum (see section 6.3.1) daily symptom cluster intensity of the last 7 days prior to visit 2.

For the modified QOLRAD, the derived clusters (see section 6.3.3) will be used, using responses at visit 2.

Missing values

If a patient answered less than 50% of the items in a cluster, the cluster score will be set to missing.

6.3.7 Symptom pattern

6.3.7.1 Modified RDQ e-diary

For the modified RDQ items and derived symptom clusters (see section 6.3.2), the following variables will be presented with descriptive statistics:

- Number of days with symptoms during the last seven days prior to visit 2
- Mean symptom intensity during last seven days prior to visit 2
- Number of morning registrations with symptoms during the last seven mornings prior to visit 2
- Mean symptom intensity during the last seven morning registrations prior to visit 2

Frequency tables will be produced for

- Number of days with symptoms reported at visit 1 (one week recall)
- Symptom intensity reported at visit 1 (one week recall)

6.3.7.2 Modified QOLRAD

Mean and SD of cluster scores at visit 1 and visit 2 will be presented.

6.3.7.3 GSRS

Mean and SD of item and dimension scores at visit 1 and visit 2 will be presented.

6.3.7.4 Most troublesome symptoms

The frequency of the “most troublesome” and the “second most troublesome” symptom reported at visit 1 and visit 2 will be presented.

6.3.7.5 HADS

Frequency and proportion of patients with dimension scores 0-7 (normal), 8-10 (mild), 11-14 (moderate), 15-21 (severe) will be presented for the anxiety and depression dimension respectively.

6.3.7.6 Impact of symptoms e-diary items

For the items with responses on an 11 point NRS and the derived clusters (see section 6.3.4), the mean value will be presented graphically by day for the last seven days prior to visit 2. A cluster score will be calculated as the mean value of the item responses in the cluster.

Descriptive statistics will be calculated for the morning report items

- How long did it take you to fall asleep last night?
- How many times did you wake up after falling asleep?
- After falling asleep for the first time, how much total time did you spend awake during the night?
- How long did you sleep last night?

6.3.8 Demographic data and disease history

The following will be presented descriptively:

- Demographic variables (age, sex, race, BMI, nicotine use)
- History of GI symptoms
- History of PPI treatment
- IBS, Rome II and III criteria
- History of paresthesiae
- Medical and surgical history

6.4 Description of analysis sets, Part 2

The analysis sets for Part 2 analyses will be described in the SAP.

6.5 Methods of statistical analysis, Part 2

6.5.1 Test retest, modified RDQ

Test-retest reliability will be investigated for the modified RDQ using Intraclass Correlation Coefficients (ICC), using subjects in a stable condition between visit 2 and 4 (see section 6.3.5.1 for definition of ICC and stable condition). The test-retest reliability intraclass

correlation coefficient (R) and a 95% confidence interval will be estimated for each derived symptom cluster of 24 h period values (see section 6.3.2). Symptom cluster scores will be defined as the mean or maximum (see section 6.3.1) daily symptom cluster intensity of the 7 days prior to visit 2 and visit 4.

In order to be included in the test-retest calculations, a patient has to have non-missing symptom cluster scores at both visit 2 and visit 4.

6.5.2 Ability to detect change

6.5.2.1 Effect size calculations

The responsiveness of the different PRO questionnaires will be analysed by calculating the effect size. Effect sizes will be determined by OTE classifications at visit 5. The classifications will be presented in the SAP.

6.5.3 Clinically meaningful change (CMC)

Anchor based approach

Patients will be classified into sub groups based on their response to the OTE assessment at the visit after the 4 weeks treatment period. The following potential definitions of a clinically meaningful change will be derived and evaluated:

- An intrapatient change from the last 7 days before first dose to the last 7 days of treatment with respect to the number of days with symptoms, below the median change observed in the subgroup of patients classified as “Moderately better” by the OTE.

- An intrapatient change from the last 7 days before first dose to the last 7 days of treatment with respect to the number of days with symptoms, below the 25th quantile and the 10th quantile of the change observed in the subgroup of patients classified as “Unchanged” by the OTE.

Further details and additional potential anchor based definitions of clinically meaningful change will be given in the SAP.

The cumulative proportion of patients by the change in the number of days with symptoms, as defined above, will be presented by OTE classification.

Distribution based approach

The following potential definitions of a clinically meaningful change will be derived and evaluated:

- Having number of days with symptoms during the last 7 days of treatment less than the 10th quantile and the 5th quantile of the number of days with symptoms during the last 7 days before first dose.

Further details and additional potential distribution based definitions of clinically meaningful change will be given in the SAP.

Details on how to handle missing data will be given in the SAP.

6.6 Sample size considerations

With 500 patients fulfilling the inclusion criteria for Part 1, it is anticipated that 450 patients will be eligible for randomisation in Part 2. Patients will be enrolled into the study until it is predicted that 450 patients will be randomised. This is considered as a sufficient number of patients to meet the objectives of the study. Sample size considerations for selected analyses described in section 6 are given below:

- The consistency of questions within the PRO domains will be evaluated by Cronbach's alpha. Assuming the coefficient is 0.7 for a cluster with 2 items, with 450 patients the length of a 95% confidence interval for Cronbach's alpha is approximately ± 0.06. The calculations are based on formulas given in (Bonett 2002).

- Test-retest reliability will be assessed by evaluating scores at different time points within stable patients. Assuming that 40% of the patients are classified as stable by OTE and a true ICC of 0.78, with 500 patients included in Part 1 of the study, a statistical hypothesis test at 5% significance level will have approximately 80% statistical power to show that the ICC is above 0.7. The calculations are based on formulas given in (Walter et al 1998).

- A commonly used responder definition in studies with PPIs is the complete resolution of heartburn, ie 7 consecutive days without heartburn. The sample size should be large enough to be able to compare the properties of complete symptom resolution to other potential responder definitions. Based on data from the study D9120C00011 with complete resolution of symptoms defined as seven consecutive days without a burning feeling behind the breastbone and/or unpleasant movement of material upwards from the stomach, with 450 patients in Part 2 of this validation study, it is expected that approximately 40 patients will achieve complete resolution of a burning feeling behind the breastbone and unpleasant movement of material upwards from the stomach.

7. STUDY MANAGEMENT

7.1 Monitoring

Prior to the first patient in the study, a pre-study visit will be conducted by a representative of AstraZeneca to:

- determine the adequacy of the facilities

- discuss with the investigators (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca and the investigator.

During the study, a monitor from AstraZeneca or a company representing AstraZeneca will have regular contacts and will conduct regular interim monitoring visits with the study site, including visits to:

- provide information and support to the investigators
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- confirm that study staff and patients are trained according to the training plan
- monitor and confirm that the site keeps a close compliance control on the e-diary recordings
- perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigators or other staff at the site needs information and advice.

7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may visit the site to perform audits or inspections, including source data verification. The purpose of an AstraZeneca 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 protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her site.

7.3 Training of staff

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.

Before the first patient is entered into the study, the investigational staff will be trained to use the COOL WBDC system by AstraZeneca personnel or delegates.

The site staff will also be trained to use the site based electronic devices, e-diaries, ePRO Web sites, perform data transfer, monitor compliance, handle queries etc and will be authorised to train patients in using the site based device and e-diary device and perform data transfer, prior to their participation in the study. The investigators are not required to complete the full level training, if they will not train subjects, nor assign nor use the electronic devices. Investigators will, however, be trained to log into the we report system and follow the procedures for navigating to the subject data for their site.

All patients will receive training in how to use the site based ePRO device before completing the modified RDQ screening instrument, and extended training in how to use the e-diaries before entering Parts 1 and 2 of the study.

The site staff will be trained to use the dECG equipment at the investigators meeting. Also a detailed user manual will be included with the dECG equipment when delivered at the site.

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 study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be submitted to and 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 submitted to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular site's Informed Consent Form, then AstraZeneca and the site'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 protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her site. 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 site must comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the Clinical Study Protocol shall prevail.

7.6 Study timetable and end of study

Before a patient'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 Ethics Committee
- Approval of the study, if applicable, by the regulatory authority

8. ETHICS

8.1 Ethics review

The final study protocol, 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 patient into the study.

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

The Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

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/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

8.3 Informed consent

The principal investigator(s) at each site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

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

- Withholding or discontinuing of any treatment
- Physical exam including dECG
- Collecting any laboratory blood or urine samples
- Testing for pregnancy (women of childbearing potential only)
- Completing the e-diary items
- Completing any other PRO instrument and/or other assessments associated with this study

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

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

8.4 Patient 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, patients 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 code and randomisation code.

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 patients' medical history.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address & telephone number
Additional local AstraZeneca representative can be found in 'Supplement A: Study Delivery Team Contacts in the Event of Emergency'		

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see section 4.4.1.5**

In case of an emergency situation, actions should be initiated according to local practice.

There is no specific antidote reversing the effects of AZD3355 so treatment should be symptomatic and supportive of vital functions.

The treatment code may not be broken unless in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the investigator will, if time and circumstances permit, contact the local monitor prior to breaking the treatment code. If the code is broken, the date and reason should be recorded and the principal investigator should sign the record (see section 3.6.2).

9.3 Procedures in case of overdose

There is no data on overdosing. All intake of AZD3355 that exceed the dosing described in the protocol is defined as an overdose.

When using the Overdose module:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

9.4 Procedures in case of pregnancy

All outcomes of pregnancy must be reported to AstraZeneca. Should pregnancy occur during the study, treatment with investigational product should be stopped and the patient should be discontinued from the study.

9.4.1 Maternal exposure

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it. The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the appropriate AstraZeneca patient safety data entry site within 30 calendar days.

The PREGREP module in the CRF is used to report the pregnancy and the Pregnancy Outcome Report, Part 2, is used to report the outcome of the pregnancy.

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Clinical Study Protocol Version 2: Appendix A	
Drug Substance	AZD3355
Study Code	D9120C00027
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

Validation of patient-reported outcome measures for the assessment of GERD symptoms and their subsequent impact on patients with a partial response to PPI treatment in a two part multi-center phase IIA study including a four week randomised, double-blind, placebo-controlled parallel-group treatment period with AZD3355, 65 mg bid as add-on treatment to a PPI

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Developn
site representative

ASTRAZENECA SIGNATURE(S)

Validation of patient-reported outcome measures for the assessment of GERD symptoms and their subsequent impact on patients with a partial response to PPI treatment in a two part multi-center phase IIA study including a four week randomised, double-blind, placebo-controlled parallel-group treatment period with AZD3355, 65 mg bid as add-on treatment to a PPI

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I agree to the terms of this study protocol/amendment

AstraZeneca Research and Develo
site representative

ASTRAZENECA SIGNATURE(S)

Validation of patient-reported outcome measures for the assessment of GERD symptoms and their subsequent impact on patients with a partial response to PPI treatment in a two part multi-center phase IIA study including a four week randomised, double-blind, placebo-controlled parallel-group treatment period with AZD3355, 65 mg bid as add-on treatment to a PPI

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representativ

SIGNATURE OF NATIONAL CO-ORDINATING INVESTIGATOR

Validation of patient-reported outcome measures for the assessment of GERD symptoms and their subsequent impact on patients with a partial response to PPI treatment in a two part multi-center phase IIA study including a four week randomised, double-blind, placebo-controlled parallel-group treatment period with AZD3355, 65 mg bid as add-on treatment to a PPI

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations

Centre No.:

Signature:

Clinical Study Protocol: Appendix B

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol: Appendix C

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix C Modified RDQ screening instrument - US English

Wording (US English) of modified RDQ screening instrument (version 1.0), (7 day recall), to be used at visits 1 and 2

Frequency items

Please answer the following questions to help us better understand the symptoms you have been experiencing over the past 7 days because of your reflux disease. For each question, please choose the answer that is most appropriate to you.

Over the past 7 days, how often did you have a burning feeling behind your breastbone?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have pain behind your breastbone?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have a burning feeling in the center of the upper stomach?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have a pain in the center of the upper stomach?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have an acid taste in your mouth?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have unpleasant movement of material upwards from the stomach?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have burping (gas coming from the stomach through the mouth)?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have hoarseness?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have cough?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have difficulty swallowing?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have a bitter taste in your mouth?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have stomach contents (liquid or food) moving upwards to your throat or mouth?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Over the past 7 days, how often did you have heartburn?
Did not have
1 day
2 days
3-4 days
5-6 days
Daily

Intensity items

Over the past 7 days, how would you rate the intensity of a burning feeling behind your breastbone?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of pain behind your breastbone?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of a burning feeling in the center of the upper stomach?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of a pain in the center of the upper stomach?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of an acid taste in your mouth?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of unpleasant movement of material upwards from the stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Over the past 7 days, how would you rate the intensity of burping (gas coming from the stomach through the mouth)?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Over the past 7 days, how would you rate the intensity of hoarseness?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Over the past 7 days, how would you rate the intensity of cough?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Over the past 7 days, how would you rate the intensity of difficulty swallowing?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of a bitter taste in your mouth?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of stomach contents (liquid or food) moving upwards to your throat or mouth?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Over the past 7 days, how would you rate the intensity of heartburn?
Did not have
Very mild
Mild
Moderate
Moderately severe
Severe

Clinical Study Protocol: Appendix D

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	2
Appendix Date	

Appendix D RDQ - RI - US English

Reflux Disease Questionnaire – RI (RDQ-RI diary)

Bedtime:

Please answer the following questions to help us better understand the symptoms you have been experiencing since waking today (from the time you wake up until the time you go to bed) because of your reflux disease. For each question, please choose the answer that is most appropriate to you.

Since waking today, how would you rate the intensity of a burning feeling behind your breastbone?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of pain behind your breastbone?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of a burning feeling in the center of the upper stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

Since waking today, how would you rate the intensity of a pain in the center of the upper stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of an acid taste in your mouth?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of unpleasant movement of material upwards from the stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of burping (gas coming from the stomach through the mouth)?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

Since waking today, how would you rate the intensity of hoarseness?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of cough?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of difficulty swallowing?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of a bitter taste in your mouth?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

Since waking today, how would you rate the intensity of stomach contents (liquid or food) moving upwards to your throat or mouth?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Since waking today, how would you rate the intensity of heartburn?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

Morning:

Please answer the following questions to help us better understand the symptoms you have been experiencing during the nighttime (from the time you go to bed until the time you wake up) because of your reflux disease. For each question, please choose the answer that is most appropriate to you.

During the nighttime, how would you rate the intensity of a burning feeling behind your breastbone?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of pain behind your breastbone?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of a burning feeling in the center of the upper stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

During the nighttime, how would you rate the intensity of a pain in the center of the upper stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of an acid taste in your mouth?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of unpleasant movement of material upwards from the stomach?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of burping (gas coming from the stomach through the mouth)?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

During the nighttime, how would you rate the intensity of hoarseness?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of cough?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of difficulty swallowing?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of a bitter taste in your mouth?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

During the nighttime, how would you rate the intensity of stomach contents (liquid or food) moving upwards to your throat or mouth?

Did not have

Very mild

Mild

Moderate

Moderately severe

Severe

During the nighttime, how would you rate the intensity of heartburn?

Did not have

Very mild

Mild

Moderate

Moderately severe

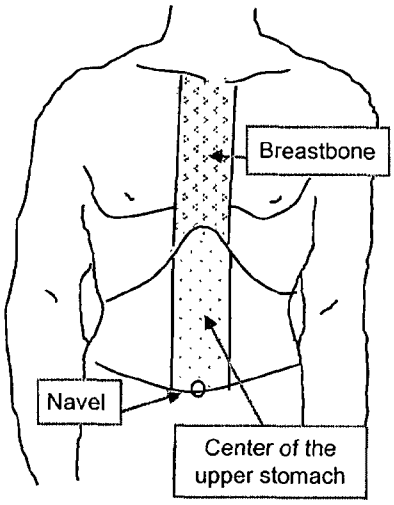
Severe

Wording to be used for twice daily symptom assessments between visits 1 and 5.

Clinical Study Protocol: Appendix E

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix E Torso picture to be used with modified RDQ - US English


Breastbone
Navel
Center of the
upper stomach

Clinical Study Protocol: Appendix F

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix F Gastrointestinal symptom rating scale (GSRS) - US English

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

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

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 MOVEMENT during 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.

AstraZeneca

Clinical Study Protocol: Appendix G

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix G SF-36v2(tm) acute recall period (SF-36v2 acute) - US English

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
☐1	☐2	☒3	☐4	☐5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐1	☐2	☐3	☐4	☐5

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

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

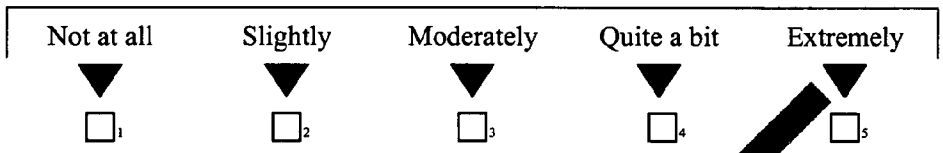
4. **During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the <u>kind</u> of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

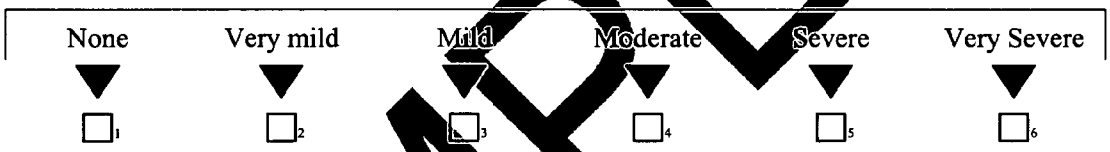
5. **During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

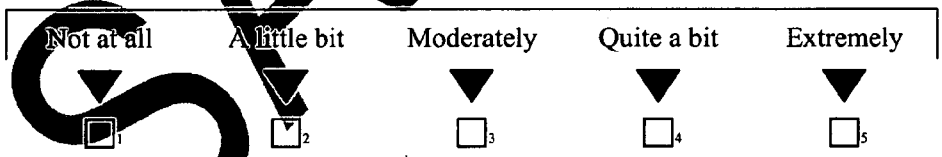
6. **During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past week</u>?**



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



9. 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
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. 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
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b I am as healthy as anybody I know	☐1	☐2	☒3	☐4	☐5
c I expect my health to get worse	☐1	☐2	☒3	☐4	☐5
d My health is excellent	☐1	☒2	☐3	☒4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

Clinical Study Protocol: Appendix H

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix H Modified QOLRAD Questionnaire for patients with symptoms of heartburn or regurgitation - US English

QOLRAD
QUESTIONNAIRE FOR PATIENTS WITH SYMPTOMS OF HEARTBURN OR REGURGITATION

PLEASE READ THIS CAREFULLY BEFORE ANSWERING THE QUESTIONS

On the following pages you will find some questions asking about how you have been feeling because of symptoms of heartburn or regurgitation.

HEARTBURN can be experienced as a burning feeling behind your breastbone.

REGURGITATION can be experienced as unpleasant movement of material upwards from the stomach, an acid or bitter taste in your mouth, or stomach contents moving upwards to your throat or mouth.

Please answer all of these questions as honestly as you can. For each question, check the box which best describes how you have been feeling DURING THE PAST WEEK.

1. How often during the past week have you been FEELING TIRED OR WORN OUT BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

2. How often during the past week did you AVOID BENDING OVER BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

3. During the past week, how much HEARTBURN OR REGURGITATION HAVE YOU HAD BECAUSE OF EATING OR DRINKING?

- ☐ A great deal
- ☐ A lot
- ☐ A moderate amount
- ☐ Some
- ☐ A little
- ☐ Hardly any
- ☐ None at all

4. How often during the past week have you FELT GENERALLY UNWELL BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

5. How often during the past week was it NECESSARY TO EAT LESS THAN USUAL BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

6. How often during the past week has HEARTBURN OR REGURGITATION KEPT YOU FROM DOING THINGS WITH FAMILY OR FRIENDS?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

7. How often during the past week did you have A LACK OF ENERGY BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

8. How often during the past week have you had DIFFICULTY GETTING A GOOD NIGHT'S SLEEP BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

9. How often during the past week has HEARTBURN OR REGURGITATION MADE IT DIFFICULT TO EAT ANY OF THE FOODS OR SNACKS YOU LIKE?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

10. How often during the past week did you FEEL TIRED OR WORN OUT DUE TO LACK OF SLEEP BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

11. How often during the past week did HEARTBURN OR REGURGITATION WAKE YOU UP AT NIGHT AND PREVENT YOU FROM FALLING ASLEEP AGAIN?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

12. How often during the past week have you felt DISCOURAGED OR DISTRESSED BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

13. How often during the past week has HEARTBURN OR REGURGITATION MADE FOOD SEEM UNAPPEALING TO YOU?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

14. How often during the past week have you FELT FRUSTRATED OR IMPATIENT BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

15. How often during the past week have you been ANXIOUS OR UPSET BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

16. During the past week, how much HEARTBURN OR REGURGITATION HAVE YOU HAD BECAUSE OF HAVING EATEN FOODS OR SNACKS YOU COULD NOT TOLERATE?

- ☐ A great deal
- ☐ A lot
- ☐ A moderate amount
- ☐ Some
- ☐ A little
- ☐ Hardly any
- ☐ None at all

17. How often during the past week have you had ANY WORRIES OR FEARS ABOUT YOUR HEALTH BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

18. How often during the past week did you FAIL TO WAKE UP IN THE MORNING FEELING FRESH AND RESTED BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

19. How much during the past week has HEARTBURN OR REGURGITATION MADE YOU FEEL IRRITABLE?

- ☐ A great deal
- ☐ A lot
- ☐ A moderate amount
- ☐ To some extent
- ☐ A little
- ☐ Hardly at all
- ☐ Not at all

20. How often during the past week have you had to AVOID CERTAIN FOOD, BEVERAGES OR DRINKS BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

21. How often during the past week did you HAVE TROUBLE GETTING TO SLEEP BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

22. How often during the past week did you FEEL FRUSTRATED BECAUSE THE EXACT CAUSE OF YOUR SYMPTOMS IS NOT KNOWN AND YOU STILL HAVE SO MUCH HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

23. How often during the past week did you have DIFFICULTY SOCIALIZING WITH FAMILY OR FRIENDS BECAUSE OF HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

24. How often during the past week were you UNABLE TO CARRY OUT YOUR DAILY ACTIVITIES (INCLUDING BOTH WORK OUTSIDE THE HOME AND HOUSE WORK) DUE TO HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

25. How often during the past week were you UNABLE TO CARRY OUT YOUR NORMAL PHYSICAL ACTIVITIES (INCLUDING SPORT, LEISURE ACTIVITIES AND MOVING AROUND OUTSIDE THE HOME) DUE TO HEARTBURN OR REGURGITATION?

- ☐ All of the time
- ☐ Most of the time
- ☐ Quite a lot of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

PLEASE CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS!

THANK YOU FOR YOUR CO-OPERATION.

Clinical Study Protocol Appendix I	
Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	2
Appendix Date	

Appendix I Impact of symptoms e-diary items - US English

Twice daily assessments between visits 1 and 5

Table 1 Morning Report Items

Item text	Response Options	Comment
Did you try to go to sleep last night?	Yes/No	
What time did you try to go to sleep last night?	HH:MM am/pm	(Not Applicable if did not try to go to sleep)
What time did you rise for the day?	HH:MM am/pm	(Not Applicable if did not rise for the day)
Did you fall asleep last night?	Yes/No	(If no, no further questions need to be answered)
How long did it take you to fall asleep last night?	Hours + Minutes	
Last night, did you wake up during the night, after falling asleep?	Yes/No	
How many times did you wake up after falling asleep?	<0-20>	
After falling asleep for the first time, how much total time did you spend awake during the night?	Hours + Minutes	
How long did you sleep last night?	Hours + Minutes	
On the following scale, what number best describes the quality of your sleep last night?	11 point NRS (0 = poor; 10 = excellent)	
How would you describe the depth of your sleep last night?	11 point NRS (0 = very light; 10 = very deep)	
Was your sleep disrupted by heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)	

Table 2 Bedtime Report Items

Item text	Response Options
The following questions are about how you are feeling and what you do because of heartburn and regurgitation.	
Since waking today, how much did you avoid eating what you wanted because of heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how much did you avoid eating when you wanted because of heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how much did your heartburn or regurgitation keep you from enjoying what you ate?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how much heartburn or regurgitation did you feel because of something you ate?	11 point NRS (0 = None at all; 10 = Very much)
Since waking today, how much did you avoid drinking what you wanted because of heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how much did you avoid drinking when you wanted because of heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how much did your heartburn or regurgitation keep you from enjoying what you drank?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how much heartburn or regurgitation did you feel because of something you drank?	11 point NRS (0 = None at all; 10 = Very much)
Since waking today, how difficult was working (including both outside the home and house work) because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)

Table 2 Bedtime Report Items

Item text	Response Options
Since waking today, how difficult were physical activities (including sport, leisure activities, and moving around the home) because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how difficult was doing things with family or friends because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how much did you avoid bending over because of your heartburn or regurgitation	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how tired did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how frustrated did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, did you feel a lack of energy because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how impatient did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how anxious did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how upset did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how worried did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how fearful did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how discouraged did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)

Table 2 Bedtime Report Items

Item text	Response Options
Since waking today, how distressed did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)
Since waking today, how irritable did you feel because of your heartburn or regurgitation?	11 point NRS (0 = Not at all; 10 = Very much)

Clinical Study Protocol: Appendix J

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix J MOS Sleep Scale - US English

Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes.....1

16-30 minutes.....2

31-45 minutes.....3

46-60 minutes.....4

More than 60 minutes 5

---

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number

of hours per night: ☐☐

How often during the past 4 weeks did you...

	(Circle One Number On Each Line)					
	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
. awaken short of breath or with a headache?	1	2	3	4	5	6
. feel drowsy or sleepy during the day?	1	2	3	4	5	6
. have trouble falling asleep?	1	2	3	4	5	6
. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
. have trouble staying awake during the day?	1	2	3	4	5	6
0. snore during your sleep?	1	2	3	4	5	6
1. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
2. get the amount of sleep you needed?	1	2	3	4	5	6

Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp. 235-259), Durham, NC: Duke University Press.

Clinical Study Protocol: Appendix K

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix K Treatment Satisfaction Questionnaire - GERD (TSQ-G) - US English

TREATMENT SATISFACTION QUESTIONNAIRE - GERD

Please read this first:

On the following pages are statements patients make about medications they have received for heartburn or regurgitation. Please read carefully, keeping in mind the medication you are currently receiving. We are interested in your feelings, both positive and negative, about the medication you are currently receiving.

Think about the medication that you have taken for your heartburn or regurgitation during the last week. How strongly do you AGREE or DISAGREE with each of the following statements?

Check the box below your response.

	Very Strongly Agree	Strongly Agree	Agree	Disagree	Strongly Disagree	Very Strongly Disagree
1. My medication allows me to sleep through the night without symptoms.	☐	☐	☐	☐	☐	☐
2. My medication allows me to do everything I want to do.	☐	☐	☐	☐	☐	☐
3. It would be ideal if I could take my medication only when I expect to have symptoms.	☐	☐	☐	☐	☐	☐
4. I am comfortable requesting specific medication from my physician.	☐	☐	☐	☐	☐	☐
5. My medication provides me enough symptom relief.	☐	☐	☐	☐	☐	☐
6. I am satisfied with the amount of money I pay for my medication.	☐	☐	☐	☐	☐	☐
7. I would strongly recommend my medication to other people with the same symptoms.	☐	☐	☐	☐	☐	☐
8. If my medication would cost twice as much, it would still be worth taking it.	☐	☐	☐	☐	☐	☐
9. My medication relieves all of my symptoms.	☐	☐	☐	☐	☐	☐
10. I expect immediate relief from my medication.	☐	☐	☐	☐	☐	☐
11. I worry about the long-term use of my medication.	☐	☐	☐	☐	☐	☐
12. I have control over my symptoms.	☐	☐	☐	☐	☐	☐

	Very Strongly Agree	Strongly Agree	Agree	Disagree	Strongly Disagree	Very Strongly Disagree
13. I am dissatisfied with the medication I am receiving for my symptoms.	☐	☐	☐	☐	☐	☐
14. My doctor knows about possible problems with my medication.	☐	☐	☐	☐	☐	☐
15. My medication gives me complete relief.	☐	☐	☐	☐	☐	☐
16. I am satisfied with the speed of relief from my medication.	☐	☐	☐	☐	☐	☐
17. I prefer a medication that I don't have to take every day.	☐	☐	☐	☐	☐	☐
18. My symptoms are completely under control.	☐	☐	☐	☐	☐	☐
19. I feel that my medication is the best one available for me.	☐	☐	☐	☐	☐	☐
20. My medication is too expensive for the relief that I get from it.	☐	☐	☐	☐	☐	☐
21. I prefer to take my medication only when I have symptoms.	☐	☐	☐	☐	☐	☐
22. I expect my medication to relieve all of my symptoms.	☐	☐	☐	☐	☐	☐
23. My medicine provides immediate symptom relief.	☐	☐	☐	☐	☐	☐
24. I am satisfied with the medication I have received for my symptoms.	☐	☐	☐	☐	☐	☐
25. I prefer taking my medication every day.	☐	☐	☐	☐	☐	☐
26. My medication allows me to eat or drink anything I want.	☐	☐	☐	☐	☐	☐
27. I worry about the side effects I have with my medication.	☐	☐	☐	☐	☐	☐
28. I am satisfied with the overall medical care I have received for my symptoms.	☐	☐	☐	☐	☐	☐

PLEASE CHECK THAT ALL QUESTIONS HAVE BEEN ANSWERED!

THANK YOU FOR YOUR CO-OPERATION.

Clinical Study Protocol: Appendix L

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	2
Appendix Date	

Appendix L Overall Treatment Evaluation (OTE) - US English

Wording (US English) of Overall Treatment Evaluation (OTE) (version 2.0), to be used at visits 2, 4 and 5

Wording of instructions when administered at visit 2:

We would like to find out if there are any changes in the way you have been feeling since you entered this study.

Wording of instructions when administered at visit 4 and 5:

We would like to find out if there are any changes in the way you have been feeling since treatment with the study medication started, i.e. the medication that you have been taking twice daily.

Wording when administered at visit 2:

Since you entered this study, has there been any change in your reflux symptoms (e.g. heartburn or regurgitation)? Better About the same Worse

Wording when administered at visit 4 and 5:

Since treatment with the study medication started, has there been any change in your reflux symptoms (e.g. heartburn or regurgitation)? Better About the same Worse

(Continues on the following page)

Wording when administered at visit 2;

if "Better"	*if "Worse"*
How much better would you say your reflux symptoms (e.g. heartburn or regurgitation) have become since you entered this study?	How much worse would you say your reflux symptoms (e.g. heartburn or regurgitation) have since you entered this study?
Almost the same, hardly better at all	Almost the same, hardly worse at all
A little better	A little worse
Somewhat better	Somewhat worse
Moderately better	Moderately worse
A good deal better	A good deal worse
A great deal better	A great deal worse
A very great deal better	A very great deal worse

Wording when administered at visit 4 and 5;

if "Better"	*if "Worse"*
How much better would you say your reflux symptoms (e.g. heartburn or regurgitation) have become since treatment with the study medication started?	How much worse would you say your reflux symptoms (e.g. heartburn or regurgitation) have become since treatment with the study medication started?
Almost the same, hardly better at all	Almost the same, hardly worse at all
A little better	A little worse
Somewhat better	Somewhat worse
Moderately better	Moderately worse
A good deal better	A good deal worse
A great deal better	A great deal worse
A very great deal better	A very great deal worse

(Continues on the following page)

Wording when administered at visit 2, 4 and 5;

if "Better"	*if "Worse"*
How important is this improvement to you in carrying out your daily activities (e.g. work outside the home, housework, normal physical activities, sport, leisure activities, etc.)?	How important is this deterioration to you in carrying out your daily activities (e.g. work outside the home, housework, normal physical activities, sport, leisure activities, etc.)?
Not important	Not important
Slightly important	Slightly important
Somewhat important	Somewhat important
Moderately important	Moderately important
Important	Important
Very important	Very important
Extremely important	Extremely important

Clinical Study Protocol: Appendix M

Drug Substance	AZD3355
Study Code	D9120C00027
Appendix Edition Number	1
Appendix Date	

Appendix M Hospital Anxiety and Depression Scale (HADS) - US English

Hospital Anxiety and Depression Scale (HADS)

nferNelson
understanding potential

Name: _____ Date: _____

FOLD HERE

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 understand how you feel. Read each item below and **underline the reply** that comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

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

FOLD HERE

A	D		A	D
		I feel tense or "wound up"		**I feel as if I am slowed down**
3		Most of the time	Nearly all the time	3
2		A lot of the time	Very often	2
1		From time to time, occasionally	Sometimes	1
0		Never	Never	0
		I enjoy the things I used to enjoy	**I get a sort of frightened feeling like "butterflies" in the stomach**	
	0	Definitely	Never 0	
	1	Not quite so much	Occasionally 1	
	2	Only a little	Often 2	
	3	Hardly at all	Very often 3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**	
3		Very definitely and fairly badly	Definitely	3
2		Yes, but not too badly	Often I don't take as much care as I should	2
1		Sometimes, but it doesn't worry me	Sometimes I don't take as much care as I should	1
0		Never	I take just as much care as ever	0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**	
	0	As much as I always could	Definitely 3	
	1	Not quite so much now	Quite a lot 2	
	2	Definitely not so much now	Not very much 1	
	3	Never	Never 0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**	
3		A great deal of the time	As much as I ever have	0
2		A lot of the time	Somewhat less than I used to	1
1		Not too often	Much less than I used to	2
0		Almost never	Rarely	3
		I feel cheerful	**I get sudden feelings of panic**	
	3	Never	Very often 3	
	2	Not often	Often 2	
	1	Sometimes	Not very often 1	
	0	Most of the time	Never 0	
		I can sit at ease and feel relaxed	**I can enjoy a good book, radio or television program**	
0		Always	Often	0
1		Usually	Sometimes	1
2		Not often	Not often	2
3		Never	Very seldom	3

Now please make sure that you have answered all the questions

	A	D
TOTAL		

HADS - United States/English - Mapi Research Institute - 3107

Clinical Study Protocol Appendix N

Drug Substance	AZD3355
Study Code	D9120C00027
Edition Number	3
Date	

Appendix N
Examples of drugs prohibited in study D9120C00027 due to their potential to prolong the QT interval*

Concomitant Medication	Class
Disopyramide	Antiarrhythmic 1A
Procainamide	Antiarrhythmic 1A
Quinidine	Antiarrhythmic 1A
Mexiletine	Antiarrhythmic 1B
Propafenone	Antiarrhythmic 1C
Flecainide	Antiarrhythmic 1C
Amiodarone	Antiarrhythmic III
Dofetilide	Antiarrhythmic III
Ibutilide	Antiarrhythmic III
Sotalol	β blocking agent III
Bepridil	Ca channel blocker IV
Metoclopramide	Prokinetic
Dolasetron	Anti-emetic
Ondansetron	Anti-emetic
Droperidol	Anti-emetic
Levomethadyl	Opioid agonist
Chlorpromazine	Antipsychotic
Haloperidol	Antipsychotic
Pimozide	Antipsychotic
Thioridazine	Antipsychotic
Risperidone	Antipsychotic
Ziprasidone	Antipsychotic
Amitriptyline	Antidepressant
Nortriptyline	Antidepressant
Protriptyline	Antidepressant
Desipramine	Antidepressant
Imipramine	Antidepressant
Venlafaxine	Antidepressant
Fluxetine	Antidepressant
Chloroquin	Anti-malarial
Pentamidine	Anti-infective

Concomitant Medication	Class
Disopyramide	Antiarrhythmic 1A
Solifenacine	Anti-spasmodic
Vardenafil	Anti-spasmodic
Erythromycin	Antibiotic
Clarithromycin	Antibiotic
Azithromycin	Antibiotic
Telithromycin	Antibiotic
Gatifloxacin	Antibiotic
Gemifloxacin	Antibiotic
Levofloxacin	Antibiotic
Moxifloxacin	Antibiotic
Ofloxacin	Antibiotic
Fluconazole	Antimycotic
Ketoconazole	Antimycotic
Tacrolimus	Immunosuppressive

*Based on US Prescribing Information