Drug Product Drug Substance Gefitinib Study Code D1450C00001 Date 21 June 2007	**SYNOPSIS**	

A 4-week randomized, double-blind, placebo controlled, parallel group, phase II study to assess the efficacy and safety of gefitinib tablets, 250 mg once daily (OD), in adult patients with moderate chronic obstructive pulmonary disease (COPD)

Study centre(s)

This study was conducted in Denmark (6 centres), Finland (2 centres), Norway (5 centres) and Sweden (4 centres).

Publications

None at the time of this report

Study dates

First subject enrolled 20 June 2006

Last subject completed 21 December 2006

Date of early study termination 15 December 2006. The study was terminated due to safety reasons.

Phase of Development

Therapeutic exploratory (II)

Objectives

Primary Objective

The primary objective of this study was to evaluate the efficacy of gefitinib tablets, 250 mg once daily (od) on symptoms, mainly cough and sputum production, in patients with Chronic Obstructive Pulmonary Disease (COPD) compared to placebo during a 4-week treatment period.

Primary Outcome variables

The main outcome variable was cough assessed by different symptom questions included in the following questionnaires; *Diary:* Clinical COPD Questionnaire (CCQ), Major Symptom questions. *Visits:* St. George's Respiratory Questionnaire (SGRQ), Community Acquired Pneumonia (CAP) questionnaire.

Secondary Objective and outcome variables

A secondary objective was to assess the effect of gefitinib on lung function by assessing Forced Expiratory Volume in one (1) second (FEV_1), Forced Vital Capacity (FVC), Vital Capacity (VC), and Inspiratory Capacity (IC), respiratory symptoms (other than cough) captured by questionnaires; Health Related Quality of Life (HRQL), SGRQ and CAP at clinical visits, as well as recorded in diaries, and Peak Expiratory Flow (PEF).

Another secondary objective was to assess safety by collecting nature, incidence and severity of Adverse Events (AEs) including obtaining Electrocardiogram (ECG), vital signs and laboratory safety assessments.

In addition, the effect on phosphorylation of the Epidermal Growth Factor Receptor (EGFR) in bronchial biopsies will be measured in a subgroup. The number of COPD exacerbations was assessed at clinical visits in all patients.

Exploratory Objectives in all patients

- To evaluate the effect on the EGFR, mucins and, inflammatory mediators measured in spontaneous sputum.
- To evaluate the effect on inflammatory mediators measured in blood.
- To collect and store tissue samples for potential future genetic research into genes which may influence the efficacy, safety and tolerability of gefitinib (optional part of this study).

- To collect blood, urine and, sputum samples for analysis of additional biomarkers that may give supplementary information on the role of the EGFR in mucus production.

Exploratory Objectives in a subgroup

A subgroup of patients underwent a bronchoscopy, where BAL (bronchoalveolar lavage) and biopsies were taken. In this group pharmacokinetic (PK) sampling also was done.

Patients participating in the subgroup in Sweden had bacterial samplings made on spontaneous sputum and, on samples taken during bronchoscopy.

- To evaluate the effect on mucins and different components in the EGFR pathway, goblet cells, in bronchial biopsies.
- To evaluate the effect on bacterial samples collected during bronchoscopy and in spontaneous collected sputum (Swedish centres only).
- To evaluate the effect on mucins, inflammatory markers and, cells in BAL.
- To evaluate drug exposure of gefitinib in plasma.
- To collect blood, urine, sputum, BAL and biopsy samples for analysis of additional biomarkers that may give supplementary information on the role of EGFR in mucus production.

Exploratory outcome variables

A number of exploratory outcome, as well as secondary outcome variables will be assessed, such as inflammatory markers in blood, sputum, BAL and biopsies. Other examples are EGFR phosphorylation, PK, bacterial analysis, and, Desmosine in urine. These variables will not be reported in this Clinical Study Report (CSR).

Study design

This was a multi-national and multi centre-study with a randomized, double-blinded, parallel-group design in patients with moderate COPD. Patients were enrolled and after a 2 week-run-in period randomized to start treatment with either gefitinib tablets, 250 mg od, or placebo during a 4-week treatment period. The patients were provided with a short-acting β_2-agonist (SABA) for symptom relief throughout the study.

Target subject population and sample size

Out-patients, male or post-menopausal women, 40-80 years of age, with a clinical diagnosis of COPD with symptoms for at least 2 years, and a history of chronic cough with sputum

production during the last year prior to study start. The patients had to be current or previous smokers with a smoking history of ≥10 pack-years, had a post-bronchodilatory FEV_1 ≥50 - <80% of predicted normal (PN), had a FEV_1/VC <70%. Patients who had used oral and/or inhaled glucocorticosteroids (GCSs) within 1 month of study start, or patients with a history of asthma and/or allergic rhinitis, were excluded from the study. It was planned to include 120-140 randomized patients in this study.

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

Gefitinib tablets, 250 mg taken once daily, orally (Batch 06-006227AZ).

Placebo tablets, matching gefitinib tablets, taken once daily, orally (Batch 06-006229AZ).

Duration of treatment

The study started with a 2-week run-in period followed by a 4-week treatment period. The study visits took place at enrolment (Visit 1), and after 2 weeks, ± 2 days (Visit 2 = randomisation) and thereafter weekly (7 days ± 1 day), Visits 3, 4, 5 and, 6.

Criteria for evaluation (main variables)

Patient reported outcomes (PROs) - see Primary Objective

Health economics (Not applicable)

Pharmacokinetic (Not applicable)

Pharmacodynamic (Not applicable)

Safety - see Secondary Objectives

Genetics

Genetic samples were collected and stored for potential future research into genes which may influence the level of exposure of gefitinib and the level of expression of the target gene, the EGFR. This research will form part of a possible future pooled analysis and will hence, not be reported as part of this study (see Appendix C in the Clinical Study Protocol).

Statistical methods

Analysis of variance (ANOVA) type analyses were performed on treatment means adjusted for baseline and country. All hypothesis testing was done using 2-sided alternatives. Differences between treatments were described using 95% confidence intervals and p-values. No adjustments for multiple comparisons were performed since the nature of the study is exploratory and the outcome variables measure different aspects of the disease. In the judgment of the efficacy of gefitinib 250 mg od no single variable was used, but an overall evaluation of all variables was considered. Efficacy results should be interpreted carefully,

bearing in mind that less than half of the planned subjects were included in the analysis due to premature study discontinuation.

Subject population

A total of 144 patients were enrolled at 17 centres in 4 countries. Of these 56 were allocated to treatment at Visit 2.

Table S1 Treatment group comparison of demographic and disease data. For categorical data, frequencies are given, for other data mean values and ranges are given

	Gefitinib 250mg od n=29	**Placebo n=27**	**All n=56**
Sex			
Male	15	21	**36**
Female	14	6	**20**
Age (yrs)	60.9	61.9	**61.4**
	48-79	45-76	**45-79**
BMI (kg/m^2)	25.1	25.5	**25.3**
	18-35	19-38	**18-38**
Time since diagnosis (yrs)[a]	3	2.5	**3**
	0-11	0-23	**0-23**
Smoking status			
Previous	6	3	**9**
Occasional	1	1	**2**
Habitual	22	23	**45**
Pack-years[a]	40	43	**40**
	12-72	23-90	**12-90**
FEV_1 (% P.N.)	58.9	60.6	**59.7**
	44-78	45-74	**44-78**
FEV_1 (% VC)	53.7	54.1	**53.9**
	33-66	42-69	**33-69**

a Median

In Table S2 the flow of randomized patients through the study by treatment group is shown.

Table S2 Patient flow

	Gefitinib 250mg od	Placebo	All
Randomized	29	27	**56**
Discontinued	9	6	**15**
-Adverse event	3	4	**7**
-Patient not willing to continue study	2	0	**2**
-Safety reasons[a]	1	0	**1**
-Other reasons[a]	3	2	**5**
Completers	20	21	**41**

a Of these 6 patients, 5 were withdrawn because the study was stopped. One investigator coded that as safety reasons, the others as other reasons. The sixth patient discontinued due to incorrect randomisation

Efficacy and pharmacokinetic results

There is no indication of an overall benefit of gefitinib as measured by average response over the whole month of treatment. Results should be interpreted with caution since the study was prematurely discontinued for safety reasons.

Pharmacokinetics has not been analysed.

Safety results

On 15 December 2006, when 56 patients of a planned 120 patients had been randomized and 38 patients had completed the study, AstraZeneca took the decision to terminate the study. This decision was as a result of the discovery of a potential safety signal of adverse events of pneumonia (n=3)/hypersensitivity pneumonitis (n=1) in 4 patients in the study. Of these 4 patients, only 2 had abnormal radiographs with infiltrates, the remaining 2 had clear lung fields during the event. There were some unusual additional features in these reports of fever, a modest raise in S-CRP and an increase in eosinophils and a protracted course. The randomized treatment for these 4 patients was unblinded on that day and they were found all to have received gefitinib 250 mg and a decision to stop the study was made.

There were no fatal SAEs in the study. A similar proportion of patients in the treatment groups discontinued due to adverse events (AEs). Although the majority of patients in both groups experienced *at least* one (1) AE, there were more serious and non-serious adverse events reported in the patients receiving gefitinib compared with placebo (Table S3). At preferred term (PT) level, the difference in reports of *pneumonia* was the most noteworthy, 4 cases vs 0 (Table S4). Compared with patients on placebo, patients receiving gefitinib more commonly experienced elevations from baseline of some laboratory values eg. B-eosinophils, liver enzymes (although in nearly all cases within the normal range and therefore the clinical

significance of these laboratory changes are unknown), S-CRP (often accompanied by AE reports), and also decreases in blood pressure from baseline to end of treatment.

Table S3 Number (%) of patients who had an adverse event in any category, and number of adverse events by category, after first dose

	Gefitinib 250mg od n=29	Placebo n=27	All n=56
Number (%) of patients who had an adverse event in each category[a]			
Any adverse events	18 (62%)	14 (52%)	**32** (57%)
SAEs	4 (14%)	1 (4%)	**5** (9%)
DAE[b]	3 (10%)	4 (15%)	**7** (13%)
Total number of adverse events[c]			
Any adverse events	64	27	**91**
Maximum intensity			
mild	33	20	**53**
moderate	26	6	**32**
severe	5	1	**6**
Max No. of AEs/patient	11	6	**11**
Causally related AEs[d]	28	6	**34**
SAEs (fatal and non-fatal)	5	1	**6**
Causally related SAEs (fatal and non-fatal)[d]	4	0	**4**
DAEs	10	6	**16**

a Patients with multiple events in the same category are counted once in each category

b Discontinuation of inv. prod./study due to AEs

c Multiple events with the same preferred term are counted once for each patient and category

d As assessed by the investigator

Table S4 **Adverse events by preferred term. Number (%) of patients with the most frequently reported AEs, sorted by decreasing order of frequency as summarized over all treatment groups**

Preferred term	Gefitinib 250mg od n=29	Placebo n=27	All n=56
diarrhoea	5 (17%)	4 (15%)	**9 (16%)**
nasopharyngitis	6 (21%)	3 (11%)	**9 (16%)**
pneumonia	4 (14%)	0	**4 (7%)**

Date of the report

21 June 2007