Clinical Study Summary Report

Sponsor: University College London (UCL)

Title of study: Development of an optimal antibiotic regime for long-term therapy in stable COPD

Sponsor code: 11/0078

EudraCT Number: 2011-001063-43

Chief Investigator: Professor J.A. Wedzicha

Study centre(s): Centre for Respiratory Medicine, Royal Free Campus, UCL

Studied period (years): 1 year 4 months (date of first enrolment): 17/02/2012 (date of last completed): 04/07/2013	**Phase of development:** Phase III

Primary Objectives: To measure and compare reduction in the concentration of lower airway bacteria (cfu/ml) in patients with COPD between three different antibiotic regimes and placebo

Secondary Objectives:

- Changes in spirometry (lung function measure) from baseline
- Changes in respiratory health status from baseline, as measured by St. Georges Respiratory Questionnaire (SGRQ).
- Respiratory health status at treatment end as measured from symptoms on daily diary cards
- Changes in general health status from baseline as measured by the EQ5D questionnaire
- Number of exacerbations recorded from date of drug issue until date of end of treatment visit (week 14) (using daily diary cards).
- Patient adherence to 13 weeks antibiotic/placebo treatment as measured by pill counts at treatment end
- Resistance to antibiotic treatment at treatment end as measured from sputum based on standard NHS procedures

Methodology: Single-blind, randomised, single centre trial comparing three different antibiotic regimes and placebo

Number of patients:
Planned: 200
Actual number enrolled and completed: 98

Diagnosis and main criteria for inclusion:

- Confirmed COPD diagnosis
- Informed Consent: Patients must give their signed and dated written informed consent to participate

- Gender: Male or female patients
- Age: ≥ 45 years of age at screening
- Produce sputum regularly (produce sputum in at least 3 months of a year)
- Able to complete questionnaires for health status and symptoms and considered able to comply with the dosing regimen.
- Severity of disease: Patients with a measured FEV1<80% of predicted normal values as determined at screening. An average of three spirometry readings will be taken.

Test product, dose and mode of administration, duration of treatment:

Moxifloxacin: an oral dose of 400 mg once daily for 5 consecutive days (i.e. days 1-5) every 4 weeks for a total duration of 13 weeks (i.e. weeks 1, 5, 9 and 13).

Azithromycin: an oral dose of 250 mg once daily three times a week (i.e. days 1, 3 and 5 of every week) for a total duration of 13 weeks.

Doxycycline: an oral dose of 100 mg once daily, for a total duration of 13 weeks.

Placebo: an oral daily dose of one tablet, for a total duration of 13 weeks.

Endpoints

Primary endpoint: Airway bacterial numbers assessed using quantitative culture analysis of (spontaneously expectorated) sputum

Secondary endpoints:

- Number of exacerbations recorded from date of drug issue until date of end of treatment visit (week 14) (measured from daily diary cards/ recorded on CRFs)
- Total and individual components separately (Symptoms, activity, impact) of SGRQ score to measure health status, each ranging from zero (no impairment) to 100 (maximum impairment).
- Respiratory health status across groups as measured from total number of symptoms in a day and prevalence of individual symptoms.
- EQ5D as a measure of health outcome.
- Lung function (spirometry) (FEV1, FVC, FEV1/FVC ratio, FEV1 as % Predicted).
- Antibiotic resistance measured from sputum based on standard NHS procedures (not resistant, intermediate, severe, resistant)
- Adherence as measured using pill counts

Statistical methods:

The primary endpoint analysis will be an intention to treat analysis and hence non-compliers will be analysed using their randomised treatment group.

Summary measures of the primary endpoint will be presented (mean, standard deviation, median, interquartile range) by treatment group and for both baseline and end of trial follow-up visits. The percentage of missing data will be summarised.

A multiple regression analysis will be conducted with lower airways bacteria counts (log transformed) at 14-weeks post-drug issue as the dependent variable, and lower airways bacteria counts at baseline (visit 1) as an independent variable All analyses will be adjusted for smoking and spirometric disease severity, both measured at baseline. A treatment

indicator will allow us to assess the treatment effect of each antibiotic relative to placebo. A Wald test will be used to judge significance of each treatment effect.
The model assumes that the dependent variable is normally distributed. This will be checked prior to analysis, and if necessary an appropriate transformation will be applied. Other goodness of fit tests, including the use of residual plots, will be conducted to ensure model validity.
Bayesian analysis, using weighted measures of efficacy, adherence, cost, bacterial resistance and side effects will be used to decide the best antibiotic to carry forward to the third work package (WP3), a longer trial of antibiotics to prevent exacerbations.

Summary – Conclusions

Efficacy: There were no statistical differences between the three active treatments compared to placebo. Moxifloxacin showed a marginally greater (non-significant) decrease in bacterial numbers compared to the other treatments.
Adherence to medications: Adherence was high in all four treatment arms (>92%) and there were no significant differences observed.
Adverse events: There were more treatment-related adverse events seen in the moxifloxacin arm than in the other treatment arms.
Bacterial resistance: No statistically significant differences were seen in induction of bacterial resistance across the treatment arms.
Cost: The costs of the treatments are fixed. Per 4 weeks of treatment, moxifloxacin costs £12.43, doxycycline £2.80 and azithromycin £9.80.

Using a weighted Bayesian analysis with the above results, doxycycline was ranked first overall out of the three treatments although the confidence intervals were wide.

Arrangements for publication or dissemination of results: The results will be written up and published in a respiratory journal once the final analysis has been completed. In the mean time work is proceeding to start the next trial using doxycycline.