SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Argenta Discovery Ltd</td><td rowspan="3">Individual Study Table
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Page:</td><td rowspan="3">(FOR NATIONAL AUTHORITY USE ONLY)</td></tr>
<tr><td>Name of Finished Product:
ADC4022</td></tr>
<tr><td>Name of Active Ingredient:
Theophylline solution for inhalation</td></tr>
<tr><td colspan="3">Title of the study:
A Phase II, Randomised, Double-Blind, Placebo-Controlled Pilot Efficacy Study of ADC4022 (Theophylline Solution for Inhalation) on Markers of Pulmonary Inflammation in Subjects with Moderate to Severe COPD (ADC4022_CLIN_02P).</td></tr>
<tr><td colspan="3">Investigators:
10 investigators took part in this study.</td></tr>
<tr><td colspan="3">Study Centres:
The study was conducted in 2 countries, United Kingdom and Poland, with 5 sites in each country.</td></tr>
<tr><td colspan="3">Publication (reference): No publications currently reference this study.</td></tr>
<tr><td colspan="2">Study period:
19 October 2007 to 30 December 2008</td><td>Phase of development: 2</td></tr>
<tr><td colspan="3">Objectives:
In this exploratory, early-stage study, the primary efficacy objective indicated in the protocol was the change from baseline in neutrophil counts (percent and absolute neutrophil counts) in induced sputum. As this endpoint is exploratory in nature, the planned analysis was changed (prior to the unblinding of the data) to add other measures of efficacy as primary objectives of the study. These endpoints were considered as measures of activity relevant to the continuation of the development of the drug, as well as to the design of future trials.
Primary objectives:
To evaluate the effect of ADC4022 (theophylline solution for inhalation) compared with placebo after 4 weeks of treatment in subjects (current and ex-smokers) with moderate to severe COPD, when coadministered with inhaled budesonide on the following parameters:
• Markers of pulmonary inflammation (percent neutrophils and absolute neutrophil counts) in induced sputum
• Pulmonary function as measured by spirometry (FEV1 [forced expiratory volume in one second], FVC [forced vital capacity], and FEV1/FVC [the ratio of FEV1 to FVC)]
• Counts of CD8+ and CD68+ cells in bronchial biopsies (for a subset of subjects)
Secondary objectives:
(1) To evaluate the effects of ADC4022 (theophylline solution for inhalation) compared with placebo, in subjects with moderate to severe COPD, when co-administered with inhaled budesonide on the following parameters:
• Pulmonary function as measured by peak expiratory flow rate (PEFR)
• Disease control as measured by exacerbation rate and use of rescue medication
• IL-8 concentration in induced sputum
• Total induced sputum cell count
• Macrophages, eosinophils and lymphocytes in induced sputum (percentage and absolute counts)</td></tr>
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• Symptoms and quality-of-life as measured by the St. Georges Respiratory Questionnaire (SGRQ)

(2) To evaluate the tolerability of ADC4022 (theophylline solution for inhalation) when co-administered with inhaled budesonide in subjects with moderate to severe COPD.

(3) To evaluate the single-dose and repeat-dose (Day 28) pharmacokinetics (PK) of ADC4022 (theophylline solution for inhalation) when co-administered with inhaled budesonide in subjects with moderate to severe COPD

Methodology:

This multicentre, double-blind, parallel-group, randomised, placebo-controlled, fixed-dose,Phase 2, pilot study was designed to evaluate the effect of ADC4022 (theophylline solution for inhalation) 12.5 mg twice daily (BID) added to inhaled budesonide 1 mg BID versus inhaled budesonide 1 mg BID alone on markers of pulmonary inflammation in induced sputum and pulmonary function tests in subjects with moderate to severe COPD. The effects of study treatment on additional markers were evaluated in bronchial biopsy specimens obtained from a subset of subjects in the study.

The study consisted of 4 periods, and the total duration of individual subject participation was approximately 11 weeks, with a maximum duration of 12 weeks. Subjects went to the study centre for up to 8 visits.

Eligible subjects were withdrawn from β-adrenergic agonists, long-acting anticholinergic agents, xanthines,and tricyclic anti-depressants for a 2-week Screening and Washout Period. Subjects who were clinically stable at the end of this period entered a 4-week Run-in Period, during which they received budesonide treatment (Pulmicort Respules® 1 mg BID) using the Pari LC Plus nebuliser system, Pari BOY SX air compressor, and expirate filter valve set. At the end of the Run-in Period, subjects were randomised to receive in addition either 12.5 mg ADC4022 (theophylline solution for inhalation) or matching placebo BID for a 4-week Double-blind Treatment Period. Each dose of ADC4022 (theophylline solution for inhalation)or matching placebo was to be administered immediately prior to budesonide using the same nebulisation equipment as used during the run-in period. Subjects were permitted to use inhaled ipratropium bromide pMDI (Atrovent®, 20 µg) as rescue medication (up to 2 puffs every 4 to 6 hours; not to exceed 12 puffs per day) for control of symptoms as needed for the duration of the study. The use of ipratropium bromide pMDI within 8 hours prior to spirometry was recorded in the CRF. Subjects were also provided with clear instructions of actions to be taken in the event of exacerbation of COPD symptoms. For all subjects, Day 0 of the study was the date of first administration of the study drug (baseline). At the end of the Double-blind Treatment Period, there was a 1-week Follow-up Period during which subjects were permitted to resume their previous inhaled medication.

Study diaries were dispensed to subjects for use throughout the study to record daily administration of study medications or any missed dose, use of rescue medication, changes in concomitant medications/therapies, AEs, visits or calls to a physician’s office, accident and emergency department visits, and hospitalisations.

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Number of subjects:
Planned: Approximately 130 subjects were planned for screening in order to randomise 92 subjects.
Screened: 236 subjects
Randomised: 91 subjects (47 in the ADC4022 group and 44 in the placebo group)
Analysed:
Modified Intent to Treat (MITT) Population: 91 subjects
Per-Protocol Population: 79 subjects
Safety Population: 91 subjects

Diagnosis and main criteria for inclusion:
Subjects aged 40 to 75 years, inclusive, with moderate to severe COPD, as defined by the American Thoracic Society and the European Respiratory Society.

Test Product, Dose, Mode of Administration, and Batch Number(s):
12.5 mg ADC4022 (theophylline solution for inhalation) BID in addition to Pulmicort® Respules® 1 mg BID by nebulisation
ADC4022 Batch Nos.: ARGr002; ARGs004
Pulmicort Batch Nos. 301565, 301728, 303724
Reference Therapy, Dose, Mode of Administration, and Batch Number(s):
Matching inhaled placebo BID in addition to Pulmicort® Respules® 1 mg BID by nebulisation
Placebo Batch Nos.: ARGr001; ARGs003
Pulmicort Batch Nos. 301565, 301728, 303724

Duration of treatment: The total duration of individual subject participation was approximately 11 weeks, with a maximum duration of 12 weeks. The Double-blind Treatment Period lasted 28 days.

Criteria for evaluation:

Primary Efficacy Variables:
Percent neutrophils and absolute neutrophil counts in induced sputum

- Spirometry: FEV1, FVC, and FEV1/FVC
- Counts of CD8+ and CD68+ cells obtained from bronchial biopsy (for the bronchial biopsy subset of subjects)

Secondary Efficacy Variables:

- Spirometry: PEFR
- Disease control as measured by exacerbation rate and use of rescue medication
- IL-8 concentration in induced sputum
- Total induced sputum cell count
- Macrophages, eosinophils, and lymphocytes in induced sputum (% and absolute counts)
- Symptoms and quality of life as measured by the SGRQ
- PK analysis: Tmax, Cmax, AUC0-8 and t½ (for the PK subset of subjects)

Exploratory Variables:
If a significant treatment benefit was found in any of the primary endpoints, further analyses of markers of inflammation were planned and these will be presented in an addendum. The following analyses are

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planned:

- Histone deacetylase 2 (HDAC2) protein expression and tyrosine nitration of HDAC2 in sputum cell pellets and HDAC2 protein expression and tyrosine nitration in sputum cell cytospins (if feasible).
- Counts of neutrophils and cells expressing HDAC2 protein obtained from bronchial biopsy (for the bronchial biopsy subset of subjects).

Safety:

Safety was assessed by examining the incidence of AEs, clinical laboratory data (haematology, blood chemistry, and urinalysis parameters), vital sign measurements (body temperature, systolic and diastolic blood pressure, heart rate and respiratory rate), physical examination findings, ECGs (PR, QRS, QT and QTc), and oropharyngeal examination.

Statistical methods:

All statistical analyses were performed using SAS® v9.1. All hypothesis testing was carried out at the 5% (2-sided) significance level unless stated otherwise. CRF data collected were presented within data listings. All data were summarised by treatment group. In addition, where appropriate, a total overall group column was included to summarise all subjects, and some data were summarised by treatment group and visit.

The mean, median, quartiles, least squares mean (LS mean), 95% confidence interval (CI), standard deviation (SD), and standard error were presented to one more decimal place than the original data.

All medications were classified using the World Health Organisation Drug Dictionary (WHODD) 20080301 coding dictionary. The Anatomical Therapeutic Chemical Classification Levels 1 to 2 was used to list and summarise the data. Previous and concomitant medications were summarised using the MITT Population.

The number (%) of subjects reporting the use of any prior medications (prior to Day 0), and the number of reports, number (%) of subjects taking each drug by ATC levels 1 to 2 and preferred term were summarised. This table was repeated for concomitant medications at randomisation.

The extent of treatment exposure was the number of days during the Double-blind Treatment Period that the subject was exposed to the study treatment. The extent of treatment exposure (days) for the study drug (ADC4022 or placebo) and for budesonide, and the number (%) of compliant subjects (compliance of 80%-120% for both study drug and budesonide) were summarised using the MITT Population.

A full protocol violation check list was produced in a separate document prior to the blinded review meeting and the final list was agreed between the Sponsor, CRO medical monitor, and CRO statistician. Subjects with protocol violations were then identified and listed. The list of major and minor protocol violations were defined during the blinded review meeting prior to breaking the treatment blind and commencing the final analysis on the final locked database and was based on the site monitoring reports, and subject evaluability review results.

<u>Efficacy:</u>

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For the primary efficacy variables, treatment comparisons were ADC4022 vs. Placebo using both PP and MITT Populations. The main population for all efficacy analyses was the PP population due to the exploratory nature of the study.

An analysis of covariance (ANCOVA) was used to compare treatment groups with respect to change in FEV1, FVC, and FEV1/FVC. The ANCOVA model included terms for treatment group, site (as a fixed effect), smoking status (current smoker vs. ex-smoker), and the baseline value as a covariate. The treatment by site interaction effect was investigated, and if found not to be statistically significant at the 10% level of significance, it was excluded from the final model. Underlying model assumptions were investigated using diagnostic statistics and graphical methods, and, if necessary, an alternative analysis technique was to be used. The LS mean and SE for each treatment group, the LS mean for the treatment difference, 95% CI for the LS mean difference, and associated p-value were presented.

A non-parametric van Elteren extension to the Wilcoxon rank sum test, stratified by site and smoking status was used to compared treatment groups with respect to change from baseline in percent and absolute sputum neutrophil counts and bronchial biopsy (CD8+ and CD68+) cell counts. The median for each treatment group, the median difference as an estimate of the difference between the population medians, 95% CI for the difference and p-value for the van Elteren test was presented.

For each parameter, the absolute values at each visit and the change from Day 0 to Day 28 were summarised for both the PP and MITT Populations. For spirometry data, changes from baseline (Day 0) to each visit in the Double-blind Treatment Period, from screening to follow-up and from end of treatment to follow-up were also presented; at screening pre-bronchodilator challenge values were summarised. Secondary efficacy variables were summarised by treatment group for the PP population.

Pharmacokinetics:

For PK summaries, arithmetic mean, geometric mean, and coefficient of variation (%CV) were used to summarise the data by treatment group for each compound and visit (PK subset of the MITT Population). A noncompartmental model was used to calculate the parameters with the linear up/log down method. Plasma concentrations <2 µg/L were treated as 0 and concentrations of ">2" were set equal to 2.

Safety:

All adverse events (AE) were classified using the MedDRA coding dictionary Version 11.1. Study-emergentAEs and treatment-emergent AEs were summarised by body system, preferred term, and treatment group. All AE summary tables showed the number (%) of subjects having at least one event and the number of events. Summaries by body system and preferred term were also presented by treatment group and severity. Data summaries were also presented for deaths, serious adverse events (SAEs) and AEs which led to discontinuation of study medication. All clinical safety and tolerability data were summarised descriptively by treatment group and listed for each subject. Laboratory values outside of the normal ranges were listed separately with comments as to their clinical significance. Vital signs (heart rate, respiratory rate, supine resting systolic/diastolic blood pressure), and ECG data (normal or abnormal and findings) were tabulated and summarised

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descriptively by treatment group. Changes in vital signs, pulmonary function tests and ECG findings between pre-dose baseline and the post-dose measurements during the Double-blind Treatment Period and between screening and follow-up,were calculated and summarised by treatment. An oropharyngeal examination was conducted at Day 0 and Day 28. Whether the examination was performed (yes/no), examination date, and any abnormalities were listed.

Summary

Efficacy results:

After 4 weeks of treatment, percentage of sputum neutrophils increased in both treatment groups. In the PP population, the median change from baseline in percent neutrophils was 8.0 percentage points for the ADC4022 group and 0.25 percentage points for the placebo group; the median difference between the groups being 5.5 percentage points. There was a reciprocal reduction in percentage macrophages in both groups (median change -0.625 percentage points in the ADC4022 group and -0.50 percentage points in the placebo group). Based on the non-parametric Van Elteren test, treatment difference in percent neutrophils between the 2 groups was not significant (p=0.089) in the PP population (n=35 in each group), but was significant (p=0.034) in the MITT population (n=38, ADC4022 and n=40, placebo).

The median change from baseline in absolute neutrophil count was 0.70 x 106/g for the ADC4022 group and 0.46 x 106/g for the placebo group; the median difference between the groups was 0.65 x 106/g which was not statistically significant (p=0.471) based on the non-parametric Van Elteren test.

In the PP population, FEV1 remained relatively stable in the ADC4022 group over the treatment period (LS mean change 0.008 litres) while there was a decline in the placebo group (LS mean change -0.134 litres). Based on the ANCOVA analysis, the difference between the 2 groups was statistically significant at Day 28 (0.142 litres, p=0.015). In the MITT population, the LS mean change in FEV1 was -0.009 litres for the ADC4022 group and -0.115 litres for the placebo group. ANCOVA comparison of treatment differences between ADC4022 and placebo groups showed statistical significance (0.106 litres, p=0.045).

Changes seen in FEV1 were also mirrored in FVC. Clinically relevant differences between the 2 treatment groups were observed. The LS mean change from baseline in FVC was -0.006 litres for the ADC4022 and -0.287 litres for the placebo group. Based on the ANCOVA analysis, there was a statistically significant (p=0.004) difference between the ADC4022 and placebo groups in the PP population.

Changes in FEV1/FVC % were minimal as the magnitude of the change in both FEV1 and FVC was similar, resulting in a small net effect on the change from baseline in FEV1/FVC % (0.1 percentage points in the ADC4022 group and 0.7 percentage points in the placebo group, p=0.591). No clinically significant changes from baseline in PEFR were observed over the 4-week treatment period in either group (15.1 ± 64.6 litres/min in the ADC4022 group and -7.3 ± 42.3 litres/min in the placebo group).

Bronchial biopsies were performed on a subset of subjects (n=30, 14 ADC4022, 16 placebo, PP population). In biopsies from the lower of the 2 airways sampled (sub-segmental carinae, airway B),

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CD68+ (macrophage) median cell counts decreased over the 4-week treatment period in both the ADC4022 and placebo groups in the PP population. The median treatment difference between ADC4022 and placebo was -4.500 cells/mm2 (95% CI= -55.001, 40.601). CD8+ (lymphocytes) median cell counts decreased in the ADC4022 group but increased in the placebo group. The median treatment difference between ADC4022 and placebo was -36.986 cells/mm2 (95% CI= -173.992, 34.479). Comparison of these values using a Van Elteren test did not show a significant treatment difference for either CD68+ (p=0.181) or CD8+ (p=0.144). In the upper airway biopsy samples (lobar carinae, airway A), CD68+ median cell counts increased over the treatment period in both the ADC4022 and placebo groups, while median CD8+ cell counts decreased in the ADC4022 group but increased in the placebo group. Treatment differences between ADC4022 and placebo were not statistically significant for either CD68+ (p= 0.981) or CD8+ (p=0.942) cell counts using the Van Elteren test. None of the biopsy analyses had sufficient power to detect any differences between treatment groups at the p≤0.05 significance level due to the low number of samples in the PP population (14 for ADC4022 and 16 for placebo).
In the PP population, changes from baseline in median total cell count in induced sputum were not significant in either group over the 4-week treatment period nor were there any significant differences observed between the groups in the other sputum markers assessed over the treatment period (lymphocytes, eosinophils or IL-8).
None of the subjects experienced any exacerbation of COPD symptoms during the study. For all visits after baseline (Day 0), significantly fewer subjects in the ADC4022 group used rescue medication when compared with the placebo group. Total SGRQ score decreased in both groups over the 4-week treatment period (-1.894 ± 7.639 in the ADC4022 group and -3.162 ± 12.921 in the placebo group).

Pharmacokinetic results:
The median Tmax was 0.5 hours for baseline and at end of treatment. Tmax ranged from 0.25 to 1.0 hours at Day 28 and the mean Cmax was 323 µg/L (range: 122.0 – 603.0 µg/L). The mean elimination half-life was as 8.9 hours (range: 4.2 – 22.0 hours) in ADC4022 group. The plasma concentration of theophylline was at peak (310.22 µg/L) at 30 minutes. Budesonide concentrations were below the limit of quantification for the majority of subjects; therefore, it was not possible to calculate parameters for analysis.

Safety results:
The side effect profile was similar in both treatment groups, with a similar incidence of subjects with TEAEs (24 [51.1%] subjects in the ADC4022 group and 22 [50.0%] subjects in the placebo group). TEAEs that were reported by ≥5% of subjects in each group included the following: headache, cough, dyspnoea, and wheezing. In the ADC4022 group, chest discomfort was an additional TEAE reported by ≥5% of subjects, and in the placebo group, viral upper respiratory tract infection and dysphonia were additional TEAEs reported by ≥5% of subjects.

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Treatment-emergent AEs considered related to study drug were also reported at similar frequencies in the ADC4022 and placebo groups (9 [19.1%] and 7 [15.9%], respectively). The most frequently reported drug-related TEAEs in the ADC4022 group were cough or productive cough (reported by 3 subjects, of mild to moderate intensity), mild dysphonia and moderate dyspnoea (reported by 2 subjects each). In the placebo group, severe and moderate cough and mild dysphonia were reported by 2 subjects each. Only 4 subjects (3 in the ADC4022 treatment group and 1 in the placebo group) discontinued the study due to a TEAE. Three subjects discontinued the study due to TEAEs that were considered possibly or probably related to study drug, and 1 subject in the ADC4022 group discontinued the study due to an SAE (pneumonia) unrelated to study drug. No deaths occurred, and no drug-related treatment-emergent SAEs were reported. There were isolated changes in the values of biochemistry, haematology, and urinalysis parameters at Day 28 compared with values at baseline; however, no trend toward increasingly abnormal results over time was noted. The frequency and direction of changes did not differ greatly between the groups. There were no notable differences or abnormalities between ADC4022 and placebo groups in changes from baseline values in vital signs, ECG parameters, and oropharyngeal examination.		
Date of report: 10 July 2009		