1. TITLE PAGE

CONFIDENTIAL

CLINICAL STUDY REPORT

Clinical Study Report Code: M/MTAST/01

Name of the Investigational product: encapsulated montelukast sodium (Singulair®, Merck & Co.)

Indication studied: mild-to-moderate allergic asthma
Phase of the study: not applicable

"A RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND, CROSS-OVER, MONOCENTER STUDY TO EVALUATE THE EFFECT OF A 7-DAY MONTELUKAST TREATMENT ON AIRWAY INFLAMMATION AND FUNCTION BY MEANS OF BRONCHOPROVOCATION WITH ADENOSINE-5'-MONOPHOSPHATE IN PATIENTS WITH MILD OR MODERATE ALLERGIC ASTHMA"
(Protocol No. M/MTAST/01; Eudract No. 2006-000334-12)

Statistical Report No.: M/MTAST/01
Date of initiation of the study: 24MAR2006
Date of early study termination: not applicable
Date of completion of the study: 14JUN2006
Date of completion of the Report: 02AUG2007

Company / Sponsor:
Almirall Prodesfarma, S.A.
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The study was performed in accordance with Good Clinical Practices (GCP) including the archiving of essential documents

2. SYNOPSIS

Name of Sponsor / Company: Almirall Prodesfarma, S.A **Name of Finished Product:** Singulair®, Merck & Co. **Name of Active Ingredients:** Montelukast	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Title of Study: A RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND, CROSS-OVER, MONOCENTER STUDY TO EVALUATE THE EFFECT OF A 7-DAY MONTELUKAST TREATMENT ON AIRWAY INFLAMMATION AND FUNCTION BY MEANS OF BRONCHOPROVOCATION WITH ADENOSINE-5'-MONOPHOSPHATE IN PATIENTS WITH MILD OR MODERATE ALLERGIC ASTHMA		
Investigators: Principal Investigator: [redacted]		
Study centre (s): Institut für Atemwegsforschung (INSAF GmbH), Biebricher Allee 34, 65187 Wiesbaden, Germany		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 24MAR2006 Date study finalised (last patient last visit): 14JUN2006	**Phase of development:** not applicable	
Objectives: • To validate the methodology of AMP challenge as a surrogate marker for the evaluation of the activity of anti-asthmatic drugs. • To assess the effect of montelukast on the provocative concentration of adenosine-5'-monophosphate (AMP) inducing a 20% decline in Forced Expiratory Volume in one second (FEV1) (referred to as PC_{20} AMP). • To assess the effect of montelukast on recovery time following AMP challenge and on non-invasive inflammatory parameters (nitric oxide measured in exhaled breath; leukotriene E4 measured in urine; differential and absolute cell counts in induced sputum and blood; eosinophil cationic protein, cys-leukotrienes and interleukin-13 measured in induced sputum and serum; interferon gamma measured in induced sputum; interleukin-4, interleukin-5, interleukin-6, interleukin-8, interleukin-10, eotaxin, monocyte chemoattractant protein-1, tumor necrosis factor alpha and vascular endothelial growth factor measured in serum).		
Methodology: Randomised, placebo-controlled, double blind, crossover, monocenter clinical trial. Following a run-in period of 7-11 days each patient received montelukast 10 mg or matching placebo for seven consecutive days (first treatment period). Each patient was administered alternating treatment in a second 7-day treatment period, with a wash-out of 7 to maximally 21 days between each treatment. Follow-up visits were performed within 3-7 days following the second treatment period.		
Number of subjects (planned and analysed): Planned: 18 Screened: 20 Randomised: 18 Completed study: 17 Discontinued study: 1 (protocol non-compliance) Evaluated for safety: 18 Evaluated for activity: 17		

Diagnosis and main criteria for inclusion:

- Male or female patients with mild or moderate allergic asthma
- No long-acting β_2 agonist within the last 48 hours or inhaled corticosteroids within 6 weeks prior to study entry.
- $FEV_1 \geq 70\%$ of predicted, and PC_{20} AMP ≤ 400 mg/ml at screening.

Test product, dose and mode of administration, batch number, expiry date:
Name: Encapsulated montelukast sodium (Singulair®), (Merck & Co.)
Administration route: Oral
Dosage form: Encapsulated tablets prepared by Almirall
Dose and regimen: 10 mg / dose once daily for 7 consecutive days
Batch number: nº 038F0058 Expiry date: 07/2006

Duration of treatment:
There were two 7-days treatment periods for each individual patient, with a wash-out of 7 to maximally 21 days between each treatment.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo
Administration route: Oral
Dosage form: Capsules prepared by Almirall
Dose and regimen: one placebo / dose once daily for 7 consecutive days
Batch number: nº 037F0057 Expiry date: 07/2006

Name of Sponsor / Company: Almirall Prodesfarma, S.A **Name of Finished Product:** Singulair®, Merck & Co. **Name of Active Ingredients:** Montelukast	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Criteria for evaluation:

Activity variables:
The effect of montelukast on PC_{20} AMP, on recovery time following AMP challenge and on non-invasive inflammatory parameters (nitric oxide measured in exhaled breath; leukotriene E4 measured in urine; differential and absolute cell counts in induced sputum and blood; eosinophil cationic protein, cys-leukotrienes and interleukin-13 measured in induced sputum and serum; interferon gamma measured in induced sputum; interleukin-4, interleukin-5, interleukin-6, interleukin-8, interleukin-10, eotaxin, monocyte chemoattractant protein-1, tumor necrosis factor alpha and vascular endothelial growth factor measured in serum).

Safety outcomes:
Adverse events, vital signs (axillary temperature, systolic and diastolic blood pressure and heart rate), physical examination, clinical laboratory tests (routine haematology, clinical chemistry and urinalysis) and 12-lead ECGs

Other variables:-
Number of withdrawals and reason for withdrawal

Statistical methods:
Analysis of both, the primary and secondary activity variables, were performed on the PP population. For each treatment (montelukast and placebo), raw and $\log_{10}$ transformed values of PC_{20} AMP and all secondary activity variables were summarised with appropriate descriptive statistics at Day 1 (pre-treatment) and Day 7 after treatment as well as changes from Day 1. The comparisons between treatments (montelukast and placebo) of the $\log_{10}$ PC_{20} AMP at Day 7 after treatment and the change from baseline (Day 1, pre-treatment) to Day 7 were carried out using an ANCOVA model. The comparison between treatments (montelukast and placebo) of all remaining secondary activity variables were carried out using the Wilcoxon signed rank test. The median statistic of the differences were estimated using the Hodges-Lehmann estimator for paired samples.

SUMMARY AND CONCLUSIONS

Activity Results:
From all activity variables, for the following parameters a potential meaningful difference (statistically significant or strong trend) of the treatment with montelukast compared to placebo was found (median of change [95% CI]):

- Recovery time was shortened by 15 min [-35.0; 0.0] (p=0.051)
- Pre-AMP level of exhaled nitric oxide was reduced by 6.2 ppb [-16.2; 2.7] (p=0.046)
- Percentage of sputum eosinophils (% of total cells) was reduced by 4.7% [-9.2; 0.5] (p=0.052)
- Levels of monocyte chemoattractant protein-1 in serum was reduced by 11.2 pg/ml [-20.1; -1.2] (p=0.026)

For the primary activity variable (PC_{20} AMP) and all other inflammatory markers, no statistically significant differences between treatments were shown.

Safety Results:
In total more patients experienced AEs during the treatment with montelukast compared to placebo (7 vs. 4), however, only two of the AEs (diarrhoe and intermittent nausea, both of mild intensity) were considered to be possibly related to the study drug. During the adminstration of placebo AEs in 3 patients (all headache) were judged as being possibly related. There were no clinically relevant findings regarding physical examination, vital signs and ECGs. No SAE occurred, no AE resulted in withdrawal, and no clinical relevant changes of laboratory parameters were observed. Overall the

adminstration of the study drug was safe and well tolerated.

CONCLUSIONS:
The overall purpose of the study was to validate the methodology of AMP challenge as a surrogate marker for the evaluation of bronchoprotective and anti-inflammatory effects of a 1-week treatment with montelukast. An additional objective of the study was to determine whether other surrogate markers of airway inflammation are as sensitive as AMP-induced BHR.

From all activity variables, for four parameters a potential meaningful difference (statistically significant or strong trend) of the treatment with montelukast compared to placebo was found:

- Recovery time after AMP challenge
- Levels of exhaled nitric oxide (pre-AMP)
- Percentage of sputum eosionophils
- Levels of monocyte chemoattractant protein-1 in serum

For the primary activity variable (PC_{20} AMP) and all other inflammatory markers, no statistically significant differences between treatments were shown.

Overall, the adminstration of the study drug was safe and well tolerated.

Based on these results, recovery time after AMP challenge demonstrated to be a more sensitive activity variable than PC_{20} AMP for the evaluation of the activity of a cys-LT_1 receptor antagonist. Recovery time may also be a suitable end-point for the evaluation of the activity of other anti-inflammatory anti-asthmatic drugs. Monitoring the levels of exhaled nitric oxide, the percentage of sputum eosinophils and the serum levels of monocyte chemoattractant protein-1 may serve as useful additional endpoints in exploratory studies evaluating anti-inflammatory drug activity in asthmatic patients.

DATE OF REPORT:
02AUG2007