Clinical Study Report (Synopse ICH E3)

Study Title:	**Influence of tiotropium bromide (Spiriva ®) plus salbutamol versus salbutamol on the mucin secretion and sputum properties in subjects with a COPD exacerbation**	
Study Acronym	TIBROMUC	
Study Sponsor-ID	KKS-95	
EudraCT No.	2006-005819-10	
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	Date	**Signature**
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1 Name of Sponsor/Company
Philipps-Universität Marburg, Karl-von-Frisch-Str. 4, 35043 Marburg

2 Name of Finished Product
Spiriva ®

3 Name of Active Substance
Tiotropium Bromide

4 Individual Study Table: Referring to Part of the Dossier (Volume, Page)
N. A.

5 Title of Study
Influence of tiotropium bromide (Spiriva ®) plus salbutamol versus salbutamol on the mucin secretion and sputum properties in subjects with a COPD exacerbation.

Study Protocol version V01 F 11.02.2007 (First final version, there were no further versions and no amendements.)

6 Investigators
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8 Publication (reference)
N.A.

9 Studied period (years): date of first enrolment, date of last completed
The study was ended prematurely (2009-10-10) because of very few patients to recruit. Only one patient was included.

10 Phase of development
Phase IV, randomized, open

11 Objectives
The primary study objective is to detect differences in the relative mucin amount between patients treated with tiotropium bromide (Spiriva ®) plus salbutamol and those treated with salbutamol alone.

The secondary study objective is to investigate the improvement of both the biophysical and transport properties of sputum in patients with acute exacerbation of COPD and the reduction of airway obstruction in the treatment groups.

12 Methodology

In the following the methods relevant for the primary and secondary study objectives are described:

To measure the relative mucin amount the protein concentration of the mucins MUC5AC and MUC5B were determined using specific rabbit antibodies. The sputum was analyzed by gel electrophoresis. The specific mucins were measured by dot blot protein analysis. Additionally the DNA content of the sputum was determined by microfluorimetry using Hoechst staining.

In order to investigate the physical properties of mucus the Viscoelasticity was measured using a AR1000 rheometer. The Cohesivity is determined using a distraction device (Filancemeter) to stretch the mucus until breaking. Finally the mucociliary clearance (MCC) is determined by using the palate of a leopard frog as a model system. After preparation the palate the transport rate of the mucus or a sputum specimen of the patients is measured.

13 Number of patients (planned and analysed)

Planned: 38 patients per treatment group
Inclusion: 1 patient

14 Diagnosis and main criteria for inclusion

Diagnosis:
An acute exacerbation of the underlying COPD was supposed if at least two of the following signs and symptoms were present: Increased sputum purulence, increased dyspnea, or increased sputum volume.

Main inclusion criteria:
Provided signed written informed consent, acute exacerbation of COPD (please refer to "Diagnosis"), hospitalized male or female subjects ≥ 35 years of age, COPD 2 or 3 according to the GOLD criteria, FEV1/FVC < 70%, 30% <= FEV1 (GOLD 3) < 50% <= FEV1 (GOLD 2) < 80% predicted, with chronic symptoms (cough, sputum production), the onset of signs and symptoms of the current exacerbation must occur within 7 days before start of evaluation. Subjects may have taken inhaled anticholinergicor β2-agonists drugs prior to the study, except tiotropium bromide. Subjects may have taken inhaled corticosteroids prior to the study.

15 Test product, dose and mode of administration, batch number

Test product: Tiotropium bromide (Spiriva ® 18 Mikrogramm, Kapsel mit Inhalationspulver)
Dosing schedule: 18 mcg; 1-0-0
Mode of administration: Inhalation

16 Duration of treatment

The planned treatment duration per patient was up to 42 days (6 weeks).

17 Reference therapy, dose and mode of administration, batch number

Reference therapy: Salbutamolsulfat (Sultanol Rotadisk ® 200 µg)
Dosing schedule: 200 mcg, 1-1-1
Mode of administration: Inhalation

18 Criteria for evaluation: Efficacy, Safety

Efficacy criteria: The primary endpoint of the study is the MUC5AC response. Patients will be considered as responders if their relative amount of MUC5AC, at 42 days after randomization, is equal to the laboratory standard level.

Safety criteria: Safety data were no relevant criteria for evaluation.

19 Statistical methods

MUC5AC response rates per treatment group will be calculated. A two-sided Chi-square test at a significance level of $\alpha = 0.05$ will be used to test for differences in response rates between the treatment groups using the intention to treat population.

20 Summary - Conclusions: Efficacy Results, Safety Results, Conclusion

Only one patient was recruited for the study. According to this there are no results available concerning the efficacy or the safety of the tested drug.

21 Date of report

2012-06-01