

**Investigation of Inhaled Prolastin® in Subjects with Cystic Fibrosis (CF2)**

<b>Title of the study:</b>	Multicenter, randomized, parallel group study to investigate the optimal deposition site for inhaled Prolastin® in patients with cystic fibrosis (CF)
<b>Publications (references):</b>	Griese M, Latzin P, Kappler M, Weckerle K, Heinzlmaier T, Bernhardt T, Hartl D. alpha1-Antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. Eur Respir J. 2007 Feb;29(2):240-50. Epub 2006 Oct 18.
<b>Period of study:</b>	16 Dec 2003 (first subject's first visit) to 24 Jun 2004 (last subject's last visit)
<b>Clinical phase:</b>	2
<b>Objectives:</b>	To determine the optimal region for deposition of A1AT by achieving a high neutralization of free elastase in the induced sputum of subjects with CF.
<b>Methodology (design of study):</b>	Multicenter, randomized breathing pattern, open treatment, parallel group study. Blinding was not feasible, because subjects and investigators could realize the different breathing patterns.
<b>Number of patients:</b>	<p>Planned: 72 (36 per treatment group);</p> <p>Enrolled and randomized: 72 (peripheral deposition group: N=37; bronchial deposition group: N=35);</p> <p>Treated with A1AT: 59 (peripheral deposition group: N=30; bronchial deposition group: N=29);</p> <p>Drop-outs: 9 of the peripheral deposition group (thereof 7 during the run-in phase), 7 of the bronchial deposition group (thereof 6 during the run-in phase). One subject in each group dropped out because of an adverse event.</p> <p>All of the treated subjects were included in the Intent to Treat (ITT) and safety analysis. Nine of the subjects of the peripheral deposition group and 11 subjects of the bronchial deposition group were excluded from the modified ITT. The primary analysis population was the mITT population, which comprised 28 subjects of the peripheral deposition group and 24 subjects of the bronchial deposition group. This population consisted of 52 Caucasian men and women (n = 26 each) aged between 14 and 42 years (median: 23.5 years; mean: 25.3 ± 8.9 years).</p>

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<p><b>Test product, dose and mode of administration:</b></p>	<p>TAL-05-00007 / Alpha<sub>1</sub>-Proteinase Inhibitor (Human) (A1AT) / Prolastin®.                  The test product was filled into the nebulizer chamber of the inhalation device (AKITA® compressor with Pari-LC® Star nebulizer) and inhaled either with the breathing pattern for peripheral or bronchial deposition (randomization). The inhalation was adjusted to the respective treatment group with a SMART CARD, programmed according to the subject's lung function.</p>
<p><b>Duration of treatment:</b></p>	<p>One inhalation per day over 4 weeks.</p>
<p><b>Criteria of evaluation:</b></p>	<p>Primary efficacy variable:</p> <ul style="list-style-type: none"> <li>• Amount of free elastase in induced sputum.</li> </ul> <p>Secondary efficacy variables:</p> <ul style="list-style-type: none"> <li>• Standard lung function parameters (FEV<sub>1</sub>, Forced Vital Capacity (FVC), FEV<sub>1</sub>/FVC, Maximum Expiratory Flow (MEF)<sub>25, 50, 75</sub>) at all visits</li> <li>• A1AT activity in induced sputum</li> <li>• Total immunoglobulin G (IgG) fragments in induced sputum</li> <li>• <i>Pseudomonas</i> load in induced sputum</li> <li>• Neutrophil number in induced sputum</li> </ul> <p>Safety variables:</p> <ul style="list-style-type: none"> <li>• Treatment emergent adverse events</li> <li>• Hospitalization/emergency room visits</li> <li>• Changes in lung function parameters</li> </ul>
<p><b>Statistical methods:</b></p>	<p>The primary efficacy variable was the absolute and percent change in free elastase in induced sputum from baseline to endpoint (value at Week 6, or after 4 weeks under treatment, or last post baseline value). The primary efficacy comparison was a two-way analysis of covariance (ANCOVA) with treatment group and center as fixed factors (main effect model) and baseline measurement of free elastase in induced sputum as co-variate in the mITT population. As the residuals in this model were not normally distributed, a non-parametric approach (Wilcoxon test of the changes in free elastase between the two breathing patterns) was used in addition.</p>



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**Summary of safety:** The overall incidence of adverse events was 33% in the peripheral deposition group and 45% in the bronchial deposition group. Thereof, 23% and 28% of the subjects, respectively, experienced treatment emergent adverse events. No serious adverse events was reported. Drug-related events occurred in 10% of the subjects each. All of the drug-related adverse events were reversible and none was severe in intensity. One subject of the peripheral deposition group discontinued from the study because of a mild and transient influenza like illness which was considered as being drug-related. Another subject of the bronchial deposition group dropped out because of a non-drug-related adverse event (hemoptysis).

17% of the subjects in the peripheral deposition group and 14% of the subjects in the bronchial deposition group experienced one exacerbation of CF each during the treatment phase. No subject experienced a serious adverse event, hospitalization, or emergency room visit.