Boehringer Tiotropium Phase 2 study results

The Phase II trial (205.339) "A randomized, double-blind, placebo-controlled parallel group study to investigate the safety and efficacy of two doses of tiotropium (2.5 µg and 5 µg) administered once daily via the RESPIMAT® device for 12 weeks in patients with cystic fibrosis" was conducted in the EU, Australia, New Zealand and the United States from September 2008 to March 2010. 510 patients were randomized, with 372 patients in the age group 12 years and above and 138 in the age group 5 to ≤11 . Objective was to evaluate the effects of 12-week treatment with tiotropium RESPIMAT® (2.5 µg q.d. and 5 µg q.d.) compared to placebo on lung function in patients with CF. Co-primary endpoints were change from baseline in FEV_1 %predicted AUC_{0-4h} and change from baseline in FEV_1% predicted trough at the end of Week 12. Secondary endpoints were FVC, $FEF_{25-75\%}$, RV/TLC, RSSQ and CFQ. Both lung function co-primary endpoints for each dose were statistically significant with a difference in FEV_1%pred.AUC_{0-4h} of 2.9 % (2.5 µg dose) to 3.4 % (5.0 µg dose) vs placebo, or a change of absolute FEV_1[L] of 62 ml in trough and 114 ml in peak (5.0 µg dose). It has to be noted that this effect was reached above standard care (all pulmonary medications were allowed beside anticholinergics) and in a study population without upper limit of FEV_1%pred at baseline. In study 205.339, FEV_1 % predicted at baseline was 95% (mean) in the younger and 70% (mean) in the older age group. Results of secondary endpoints were generally supportive.

The study demonstrated a similar safety profile to that observed in study 205.338 over the 12 weeks of the trial. Adverse Events (AE) and Serious Adverses Events (SAE) were balanced between groups and did not reveal any specific concerns, especially for AEs of interest in CF (e.g. DIOS).

The exposure (based on $C_{0.083,ss}$ and $Ae_{0-4,ss}$) to tiotropium increased slightly less than dose proportional with increasing dose. CF patients ≤11 years old showed comparable, but slightly lower tiotropium plasma concentration as compared to CF patients ≥12 years. The exposure (based on $C_{0.083,ss}$ and $Ae_{0-4,ss}$) were comparable, but slightly lower in CF patients as compared to historical data of COPD patients

The 5 µg dose showed a higher effect than the 2.5 µg dose for FEV_1%pred AUC_{0-4h} driven by the age group 11 years and below. Based on data obtained in a Phase II study (205.339) in CF patients (efficacy, PK and safety) the proposed daily dose in this trial is 5µg tiotropium.