Title of Study

A double-blind, randomised, placebo-controlled trial to evaluate tolerability, safety and efficacy of AKITA JET Inhaled Steroid Suspension (AICS) for inhalation in subjects with asthma requiring chronic oral corticosteroid treatment

Study Period		**Phase of Development**
Date of first enrolment	04 March 2010	2b/3
Date of last completed	15 August 2011	

Objectives

Efficacy, safety and airway tolerability of AICS-Budesonide (AICS-Bud) in subjects with asthma requiring chronic oral corticosteroid treatment

Methodology

Double-blind, randomised, parallel, placebo- and active-controlled trial

Number of Subjects (Planned and Analysed)

Planned: 195 subjects

Actual: 220 subjects screened, 200 subjects randomised, 199 subjects were evaluated for efficacy and safety, i.e. 80 subjects on AICS-Bud 1 mg, 40 subjects on AICS-Placebo, 39 subjects on AICS Bud 0.5 mg and 40 subjects on Conventional Nebuliser (CN) -Bud.

Criteria for Inclusion

To participate in the study, subjects had to meet the following main inclusion criteria:

1. Written informed consent prior to the performance of any study-related procedures.
2. Age $\geq$ 18 and $\leq$ 65 year of age.
3. Diagnosis of asthma (ATS definition, either allergic or non-allergic) for $\geq$ 6 months.
4. Asthma treated for at least 3 months with ICS and OCS with a minimum of at least 5 mg/day OCS, up to a maximum of 40 mg/day or 80 mg/day if taken every other day. Exact baseline level of OCS and SABA were measured during the screening period by subject diary entries.
5. $FEV_1 \geq 40\%$ or $\leq 79\%$ predicted at the screening or baseline visit.
6. Documented increase of at least 12% in absolute FEV_1 within 15-30 minutes after the use of inhaled salbutamol at the screening visit or within 2 years prior to screening.
7. Mandatory usage of long-acting β-agonists.

Subjects were excluded if they met any of the following **main** exclusion criteria:

1. History of allergy or adverse experience with budesonide.
2. Upper respiratory tract infection within 4 weeks of screening.
3. Emergency room visit for treatment of asthma exacerbation within 4 weeks of screening.
4. Hospitalisation for asthma within 3 months of screening.

5. Use of anti-IgE, methotrexate, oral gold, Dapsone, or i.v. gamma globulin within 3 months of screening.
6. Treatment with other investigational asthma treatment within 30 days prior to screening.
7. Evidence of chronic lung diseases other than asthma, including but not limited to: cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA), COPD, chronic bronchitis and emphysema.
8. OCS average daily dose of >40 mg/day or >80 mg/day if taken every other day.
9. Taking oral or i.v. corticosteroids for any disease indication other than asthma.

Test Product, Dose and Mode of Administration

AICS-Bud 1 mg (1 mg/2 ml budesonide; BID); AICS-Bud 0.5 mg (0.5 mg/2 ml budesonide; BID)

Duration of Treatment

18 weeks

Reference Therapy, Dose and Mode of Administration

Comparator 1 (double blind): AICS-Placebo (0.9% saline, 2 ml, BID)

Comparator 2 (open): Conventional Nebuliser-Bud (1 mg/2 ml budesonide, BID; Pari LC SPRINT)

Criteria for Evaluation

Efficacy

The primary efficacy endpoint was the reduction in OCS daily dose at Week 14 by ≥50% from baseline (Day 0) and the subject's ability to remain clinically stable for ≥4 weeks from the final taper (Week 14) to the end of the treatment period (Week 18).

Secondary efficacy endpoints:

- percentage of subjects completely weaned off OCS by Week 18
- change and percentage of change in FEV_1 (L/s) from baseline
- changes in FEV_1% predicted from baseline
- mean reduction of OCS (mg) from baseline to Week 18
- number and percentage of subjects with asthma exacerbations or instability
- time to asthma exacerbation or instability
- change in average number of puffs of salbutamol per day from baseline
- change in AQLQ scores
- changes in peak flow rates and asthma symptom scores
- change and percent change in number of nocturnal awakenings from baseline
- number of days of hospitalisation
- absenteeism from work/school
- budesonide levels at baseline and at Week 18

Safety

The safety evaluations included analyses of adverse events (AEs), hospitalisations, emergency room visits, laboratory parameters, vital signs, body weight, body mass index, and physical examination. The analysis of safety was based on the safety set.

The analysis of AEs included only treatment-emergent events, i.e. only events which were not present prior to study drug administration or which increased in intensity after study drug administration. All other AEs were listed only.

Statistical Methods

The study was conducted using a two-stage group sequential adaptive design with potential sample size adjustments after the planned interim analysis.

The primary objective was to demonstrate superiority of AICS-Bud compared to placebo. The primary efficacy variable was subjected to a confirmatory statistical analysis (experiment-wise type I error rate $\alpha = 0.025$, one-sided). The null hypothesis, $\pi T \leq \pi P$ (T denoted 1 mg budesonide, P denoted placebo), was tested by means of the $\chi 2$ test and ADDPLAN.

Evaluations of secondary efficacy variables were pre-defined in the study protocol and the SAP and performed with descriptive methods and appropriate tests and comparisons were done to estimate the effect size (experiment wise type I error rate $\alpha = 0.05$, two-sided).

Summary – Conclusions

Efficacy Results

Demographic and baseline characteristics revealed no significant differences between the treatment arms and were considered well balanced across treatment arms at study start.

78% of the study subjects were receiving an OCS dose 5-10 mg/day and 22% were receiving >10- 40 mg/day at study start. The distribution of OCS dose across these subgroups was similar across all treatment arms. At study start, the treatment arms were found comparable with regard to the subjects' asthma history, FEV_1 and FEV_1% predicted, morning and evening PEF, the MiniAQLQ® total score and subscores, number of rescue puffs and the concomitant medications.

The analysis of the primary endpoint (proportion of subjects reducing their daily OCS dose by ≥50%) revealed that AICS-Bud 1 mg was superior to AICS-Placebo (80.0% versus 62.5%, one-sided p- value = 0.0220, confirmatory). AICS Bud 1.0 mg was not superior to CN-Bud (80.0% versus 75.0%).

A number of secondary efficacy endpoints were evaluated:

- For AICS-Bud 1 mg, OCS weaning resulted in a reduction of approximately 75% of OCS dose from baseline to Week 18. This was achieved with the AICS-Bud therapy being "added on" to maximal asthma standard of care.
- The number of subjects fully weaned off OCS was greater for AICS-Bud 1 mg when compared to AICS-Placebo (56.3% versus 42.5%).
- AICS-Bud 1 mg showed clinically meaningful benefits in lung function, exacerbations and QoL, as determined by a 16.5% improvement in FEV_1 at 18 weeks

(vs. 6.2% on placebo), 1.6 puffs reduction in salbutamol use (vs. 0.4 on placebo), and 0.83 points improvement in the MiniAQLQ® total score (vs. 0.37 on placebo).

- Increases in FEV_1% predicted and peak flow from baseline in subjects in the AICS-Placebo vs. AICS-Bud 1 mg were not statistically significant.
- The endpoints of exacerbations (AICS-Bud 1 mg: 7.5%; AICS Bud 0.5 mg: 7.7%; AICS-Placebo 17.5%; CN-Bud 22.5%) and asthma instability (defined as first OCS increase according to protocol stability/tapering criteria; AICS-Bud 1 mg: 15%; AICS-Bud 0.5 mg: 12.8%, AICS-Placebo 30%; CN-Bud 25%) demonstrated a clear and significant superiority of AICS-Bud over AICS-Placebo.
- Seven subjects in the full analysis set (FAS) database reported hospitalisations for asthma (AICS-Placebo four subjects, all active treatment one subject).
- Absenteeism from work/school was reported by two subjects in the entire FAS, 1 subject in the AICS-Placebo treatment arm was absent over 25 days and 1 subject in the AICS-Bud 0.5 mg treatment arm was absent over 22 days.
- Evaluation of the temporal trend of budesonide serum levels indicated that serum budesonide did not accumulate over the 18-week treatment period.

Safety Results

TEAEs were reported in 124 of the 199 subjects (62.3%). TEAEs were observed in 63.8% of AICS- Bud 1 mg subjects, 65.0% AICS-Placebo subjects, 51.3% of AICS-Bud 0.5 mg subjects, and 67.5% of CN-Bud subjects. Infections and infestations were the most frequently reported TEAEs (43.8%, 35.0%, 38.5%, and 37.5% for AICS-Bud 1 mg, AICS-Placebo, AICS-Bud 0.5 mg, and CN-Bud, respectively). Respiratory, thoracic and mediastinal disorders were reported in 15.0% AICS-Bud 1 mg subjects, 32.5% AICS-Placebo subjects, 12.8% AICS-Bud 0.5 mg subjects, and 25.0% CN-Bud subjects.

Further evaluation of the TEAEs with regard to severity, seriousness and causal relation to the study drug revealed no disadvantage for the treatment arms with active treatment compared with the AICS-Placebo. Among all reported serious TEAEs, a pseudomonal lung infection in a subject from the AICS-Placebo arm was the only TEAE assessed as treatment-related. Two fatal adverse events (subarachnoid haemorrhage, pulmonary haemorrhage) occurred in the treatment arm using the CN- Bud. Both TEAEs were assessed as not related to the study drug.

In this study, the drop-out rate due to study medication-related adverse events was extremely low with only 1 drop-out in the AICS-Bud 0.5 mg arm and 2 drop-outs in the AICS-Placebo arm.

Potential local adverse reactions to ICS (i.e. candidiasis, dysphonia, dyspnoea, and cough) were below the prevalence of candida and oropharyngeal side effects reported for conventionally applied inhaled steroids (<10% for fluticasone propionate).

The analysis of the safety data revealed no differences between the active treatment arms and AICS-Placebo, particularly with regards to oropharyngeal side effects and tolerability. In fact, the observed frequencies for oral candidiasis/fungal infection were lower than described in literature.

Laboratory analyses of parameters of haematology and clinical chemistry revealed no particular risks and no differences between the treatment arms. The same applied for the vital parameters.

Baseline serum morning cortisol levels indicated that a proportion of severe asthma patients entered the study with a suppression of their HPA axis. In the CN-Bud arm, endogenous cortisol increased over time possibly indicating that the achieved reduction in OCS dose over time led to reduced cortisol suppression in combination with a less effective lung deposition of CN-Bud compared to AICS treatment arms.

The urine cortisol creatinine ratio remained almost unchanged in the three active treatment arms and increased slightly in the placebo arm.

Conclusions

The totality of the efficacy, safety and PK results from AICS-001 demonstrated that AICS-Bud efficacy was achieved by effectively weaning OCS, significantly improving pulmonary function and improving QoL without the risk of exacerbations or hospitalisations (which was not the case with the CN-Bud). It is important to interpret these results in the context of the specific weaning protocol, in which OCS weaning was only done when all of three criteria were fulfilled (pulmonary function, symptoms, beta-agonist use). Additionally, all patients were maximally treated with pre-existing asthma therapies when entering the study, including ICS/LABA (inhaled corticosteroids/long acting beta-agonist) combinations. These latter points are reinforced by the fact that all inhaled therapies (via metered dose inhalers (MDI) and dry powder inhalers (DPI)) remained unchanged during the study, i.e. maximal asthma therapy, the "standard of care" continued to be effective. In this study, the observed superiority of AICS-Bud 1.0 mg over AICS-Placebo was clinically meaningful, as AICS-Bud 1 mg was able to overcome a substantial placebo response rate of 62.5% in patients with severe, OCS-dependent asthma.

Since the generation of the original study report, Activaero GmbH has been acquired by Vectura.