Title of Study

A randomised, double-blind, placebo-controlled, parallel group, dose-ranging study to evaluate the efficacy and safety of three strengths of fluticasone propionate inhaled from a new dry powder inhaler in adolescent and adult subjects with asthma

Study Centre

Subjects were screened by 76 investigators at 76 sites in five countries: the Philippines (6 investigators/sites), Poland (18 investigators/sites), Romania (8 investigators/sites), Ukraine (15 investigators/sites), United States (29 investigators at 29 sites)

Study Period		**Phase of Development**
Date of first screening	12 October 2011	2b
Date of last completed	9 May 2013	

Objectives

Primary Objective

To evaluate the clinical efficacy of three strengths of Fluticasone Propionate (FP) Inhalation Powder taken twice daily from a new dry powder inhaler (nDPI) for 12 weeks in comparison with placebo to facilitate dose selection for further development.

Secondary Objectives

- To evaluate the safety and tolerability of three strengths of Fluticasone Propionate Inhalation Powder in subjects with asthma;
- To evaluate the dose-response relationship for efficacy and safety of Fluticasone Propionate Inhalation Powder.

Methodology

All subjects underwent a Screening Visit 7 to 14 days before the start of the Run-In Period. During the Screening Period, the subjects completed an electronic diary (eDiary) twice daily to record information including asthma symptoms, peak expiratory flow (PEF), forced expiratory volume in one second (FEV_1), rescue medication use (i.e. albuterol/salbutamol), and disruption of normal daily activity (e.g. ability to work, attend school).

Subjects who fulfilled the Enrolment Criteria progressed to a Run-In Period of at least 2 days and up to 6 weeks, during which time they stopped taking their usual inhaled corticosteroid (ICS) and other regular maintenance therapies. They continued to record asthma symptoms, PEF, FEV_1, rescue medication use and disruption of normal daily activity in the eDiary twice daily. They visited the clinic weekly during the Run-In Period for assessment of asthma control and to see whether they met the randomisation Entry Criteria of 10-25% reduction in FEV_1 and ability to use the nDPI. At any time during the Run-In Period, if the subject complied with the randomisation Entry Criteria based on in-clinic spirometric measurements, he/she was entered into the Treatment Period and randomised to receive one strength of

Fluticasone Propionate Inhalation Powder (50, 100 or 250 µg) or placebo twice daily. In addition to the scheduled weekly visits during the Run-In Period, the eDiary was programmed to issue an alert if the eDiary readings indicated worsening of asthma and suggested compliance with the randomisation FEV_1 Entry Criterion; the subject then attended the clinic for confirmatory assessment of lung function and compliance with the randomisation Entry Criteria.

Following randomisation, the first dose of study drug was administered in the clinic. Subjects continued to take one actuation of the same strength of study treatment twice daily for 12 weeks. During the Treatment Period, the subjects continued twice daily eDiary recording of asthma symptoms, PEF, rescue medication use and disruption of normal daily activity, and returned to the clinic for assessment at Weeks 1, 4, 8 and 12.

Safety assessments were performed throughout the Run-In and Treatment Periods. Subjects were directed to seek medical advice should they have asthma-related problems at any time during the study. Potential suppression of the hypothalamic-pituitary-adrenal axis during the Treatment Period was evaluated by measurement of 24-hour urinary cortisol on 2 occasions (start of Week 3 of the Run-In Period and during Week 12 of the Treatment Period).

The investigator contacted the subject 7-10 days after study completion to ensure that the subject had resumed appropriate medical care and asthma treatment. The last patient last visit was defined as this contact with the last subject in the study. Subjects with adverse events (AEs) that were ongoing at the end of Week 12 or at withdrawal from the study were followed as appropriate until the AEs resolved or stabilised, up to a maximum of 30 days after the last dose of study drug.

Number of Subjects (Planned and Analysed)

Planned:

The number of subjects enrolled was to be adjusted to ensure that 320 subjects were randomised and received at least one dose of study drug (80 subjects per treatment arm). The study population was to include approximately 5% adolescents (but not more than 20%). The randomisation was to be stratified by age group to ensure similar numbers of adolescents were entered into each arm of the study.

Analysed:

A total of 853 subjects were screened, of whom 541 from 71 sites entered the Run-In Period, 374 were randomised and 373 received at least one dose of study drug (92-95 subjects per treatment group). Adolescents made up 13-15% of subjects in each treatment group.

The number of subjects screened was higher than planned because as the study progressed, the observed screen failure and run-in failure rates decreased more than expected. In addition, there was an overall increase in recruitment rates across countries.

Diagnosis and Main Criteria for Inclusion

Adolescents aged 12 to 17 years (inclusive) and adults aged 18 to 65 years (inclusive) with a documented clinical history of asthma.

Test Product, Dose and Mode of Administration

The test product was Fluticasone Propionate Inhalation Powder. Three product strengths (50, 100 and 250 μg) were used. One actuation was self-administered by inhalation, twice daily.

Duration of Treatment

All subjects received treatment for up to 12 weeks with twice daily dosing of Fluticasone Propionate Inhalation Powder or placebo.

The total maximum study duration, including the Screening Period (7-14 days) and Run-In Period (2 days to 6 weeks), was 20 weeks.

Reference Product, Dose and Mode of Administration

Placebo (inhalation grade lactose) was administered by inhalation via the nDPI, twice daily.

Criteria for Evaluation

Efficacy:

The efficacy of Fluticasone Propionate Inhalation Powder was evaluated by comparison of the following endpoints in the three active treatment groups with those in the placebo group.

Evaluation of the dose-response relationship (secondary objective) was based on comparison of these endpoints between the three active treatment groups.

The primary efficacy endpoint was:

- Mean change from Start-of-Treatment Baseline for in-clinic morning pre-dose FEV_1.

The key secondary efficacy endpoints were:

- Withdrawals due to worsening asthma;
- Mean change from Start-of-Treatment Baseline for eDiary pre-dose PEF;
- Number and severity of asthma exacerbations, and time to first exacerbation.

Safety:

The safety variables were:

- Vital signs;
- Physical examination;
- Oropharyngeal examination to assess potential fungal infection (candidiasis);
- 12-lead electrocardiogram (ECG);
- 24-hour urinary cortisol (in subjects with Run-In Period ≥2 weeks and who completed the 12-week Treatment Period);
- Standard haematology and biochemistry;
- Serum potassium and glucose (specific tests in Weeks 4 and 8 of Treatment Period);
- AEs and serious adverse events (SAEs);
- Withdrawals for reasons other than asthma exacerbation;
- Concomitant medications.

Statistical Methods

The primary aim of the study was to demonstrate absolute efficacy for each dose strength of Fluticasone Propionate Inhalation Powder studied compared with placebo in terms of change for in-clinic morning pre-dose FEV_1 from Start-of-Treatment Baseline to last study visit. The study was sized accordingly, and assuming a mean difference in morning pre-dose FEV_1 in favour of the active of ≥250 mL, a standard deviation (SD) of 0.5 L, a significance level of 5%, and 80% power, 64 evaluable subjects per treatment arm were required to meet the primary efficacy study endpoint. Allowing for 20% drop-out during the Treatment Period, 80 subjects were to be randomised to each treatment arm.

All efficacy analyses were performed for the Full Analysis Set (all randomised subjects who had at least one post-dose efficacy assessment), and for the Per Protocol (PP) population (subjects in the Full Analysis Set who participated in the study according to the protocol, i.e. without major protocol violation).

The primary efficacy analysis was a set of three ordered tests for superiority of 250, 100 and 50 µg Fluticasone Propionate Inhalation Powder over placebo by means of analysis of covariance (ANCOVA) for the mean change from Start-of-Treatment Baseline to the last study visit in morning in-clinic pre-dose FEV_1.

A key secondary aim of the study was to assess the dose-response relationship for efficacy of Fluticasone Propionate Inhalation Powder. The ANCOVA model used for the primary efficacy analysis was also used descriptively to test for differences between each product strength with respect to the primary efficacy variable (in-clinic morning pre-dose FEV_1), and eDiary morning pre-dose PEF (secondary efficacy variable). Withdrawals due to worsening asthma use were tested by Fisher‟s exact test.

Fisher‟s exact test and Cox proportional hazards model were used for analysis of asthma exacerbations and time to first asthma exacerbation, respectively.

Safety endpoints: All available data for the safety set were included in the safety database, which was analysed descriptively.

Summary Results

Demographic characteristics were generally comparable between treatment groups and compliance to study treatment was similar across treatment groups (96-97%).

A general trend in destabilisation of asthma was observed in all variables over the Run-In Period.

Efficacy Results

Considering the primary efficacy endpoint, there was a clinically and statistically significant difference in increase in FEV_1 from baseline to the end of study in all active treatment groups compared to placebo (p=0.013 in the 50 µg FP group and <0.001 in the 100 µg FP and 250 µg FP groups) for the Full Analysis Set. Similar results were obtained for the PP Set.

Analysis of key secondary efficacy endpoints showed that there were no statistically significant differences between active treatment groups in the mean change from Start-of-Treatment Baseline to last study visit for in-clinic morning pre-dose FEV_1. Although there were numerical differences and a trend in dose response was observed in the PP Set, no statistically significant differences were observed between active treatment groups. Changes in weekly average morning pre-dose PEF baseline to end of study were statistically significantly higher in the active treatment groups than in the placebo group (mean for FP groups 24.7 ± 53.5 L/min, p<0.01) and all active treatment groups had statistically significantly fewer withdrawals due to worsening asthma than the placebo group ($p \leq 0.01$ for all active treatment groups), in both the Full Analysis and PP Sets. Statistical testing showed no significant differences between active treatment groups in either parameter.

A statistically significant reduction in the number of asthma exacerbations was observed in those who received 250 µg FP (p=0.006 and 0.002, for the Full Analysis and PP Sets respectively) and the number of moderate and severe exacerbations was statistically significantly less in those who received 50 µg and 250 µg FP (p=0.014 and 0.002, and p=0.013 and ≤ 0.001 for the Full Analysis and PP Sets respectively). Considering asthma exacerbations, there was an overall treatment effect for the time to first exacerbation and the time to the first moderate or severe exacerbation (p=0.017 and 0.005, and p=0.007 and 0.002, for the Full Analysis and PP Sets respectively).

Safety Results

The majority (78%) of randomised subjects completed the study.

The proportion of subjects who experienced TEAEs was higher in the placebo (52%) than the active treatment groups (35-45%). The majority of TEAEs were reported to be mild or moderate in severity and associated with respiratory, thoracic and mediastinal disorders, mainly asthma exacerbations or worsening of asthma. The majority of severe TEAEs (all asthma) were experienced by subjects in the placebo group (56% subjects), with only four considered to be related to study drug (two subjects in the placebo group and two in the 100 µg FP group).

Two subjects experienced SAEs, one in the 50 µg FP group and the other in the 100 µg FP group. Neither was related to study treatment and both had resolved by the end of the study. None of the TEAEs led to death or resulted in persistent or significant disability or incapacity. The majority of TEAEs which led to withdrawal were asthma exacerbations or worsening of asthma.

No safety concerns were raised after assessment of vital signs and ECGs. There was no clinically significant change in the safety laboratory parameters in any treatment group over the treatment period. For 24-hour cortisol, the small number of subjects from whom data was obtained and the variability of results made the data difficult to interpret and no conclusions can be drawn.

Summary - Conclusions

Absolute efficacy, as measured by increased FEV_1, was demonstrated for each dose strength of Fluticasone Propionate Inhalation Powder studied compared with placebo, satisfying the primary objective for the study. The absolute increase in FEV_1 was clinically meaningful.

The results of the primary variable analysis were supported by the key secondary endpoints which showed significantly improved weekly average morning pre-dose PEF and fewer withdrawals due to worsening asthma compared with placebo. The benefit in lung function was accompanied by fewer exacerbations and increased time to the first moderate or severe exacerbation.

One of the secondary objectives for this study was the evaluation of the dose-response relationship of FP. Overall, no statistically significant differences were demonstrated between the active FP treatment groups. However, there was a numerical trend in the magnitude of improvements observed with increasing doses. In particular, the 250 µg FP dose demonstrated additional improvements relative to the 50 µg and 100 µg doses for the number and severity of asthma exacerbations.

There were no safety concerns during the study.

In conclusion, FP, delivered via the new dry powder inhaler was clinically effective and well-tolerated over the 12-week treatment period in mild to moderate asthmatics. Key secondary endpoints provide evidence of increasing efficacy in treating asthma over the dose range of FP studied.