The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: ELR100710

Title: A study to validate key therapeutic targets and biomarkers during allergen exposure in subjects with Allergic Rhinitis (AR).

Rationale: The recent performance of novel anti-inflammatory drugs in AR in the clinic has prompted a renewed effort to improve the selection and validation of new targets. In some instances, this process may previously have been too reliant upon literature reports. Similarly, target validation in the nose may have been extrapolated from data available in the asthmatic airway which could be of great significance given the variable phenotype in both conditions and the presence of potentially important physiological differences between asthma and AR (e.g. airway hyperresponsiveness (AHR), remodelling). Finally, the representation and importance of relevant targets/mechanism in human challenge models used for Proof of Concept (PoC) studies -particularly allergen challenge- was not known. Therefore generating well-characterised human samples from this model would increase confidence around target selection.
The aim of the study is to support the hypothesis that a molecular target plays a key pathophysiological role in the nasal allergic response. Evidence to support this hypothesis will be derived from three specific questions:

1. *Is the expression of a target (and/or related effector molecules) in the nose significantly modulated following exposure to allergen?*
2. *Is there an association observed between target expression and (i) clinical markers of the allergen response (e.g. symptoms, nasal airflow) and/or (ii) biological indices of inflammation (e.g. inflammatory mediator release, cell recruitment)?*
3. *Are changes in target expression appropriately modulated by treatment with corticosteroid?*

Phase: IIa

Study Period: 05Apr05-06May07

Study Design: This was a randomised, double-blind, placebo controlled, parallel group study.

Centres: One center in the Netherlands and one center in the United Kingdom.

Indication: Allergic rhinitis.

Treatment:
Subjects were randomised into one of three groups:

- Group 1 (Fluticasone Proprionate (FP) + Allergen) received 7 days of FP aqueous solution (2 sprays of 50 μg to each nostril, twice daily (BID)) followed by intra-nasal allergen challenge.
- Group 2 (Placebo+ Allergen) received 7 days of placebo (2 sprays to each nostril, BID) followed by intra-nasal allergen challenge.
- Group 3 (Placebo+ Vehicle) received 7 days of placebo (2 sprays to each nostril, BID) followed by intranasal vehicle challenge.

Objectives:
Primary

- To examine the change in expression of key allergy targets in the nose following exposure to allergen.
- To evaluate the effect of intranasal corticosteroids treatment on the change in target expression following allergen challenge.
- Identify biomarkers associated with clinical response to allergen and corticosteroids.

Secondary

- Examine the relationship between changes in target expression and clinical measures of allergen response.
- Identify nasal and systemic biomarkers associated with changes in target expression and with the clinical response to allergen and corticosteroids.

- Evaluate nasal pathology following allergen challenge and corticosteroid treatment.

Statistical Methods:

Sample size consideration: A total of 48 subjects were planned to be recruited for this study. The sample size was based on logistical considerations with a desire to gain further information on target expression/validation and was not powered to detect statistically significant differences. All statistical analysis is therefore deemed to be exploratory in nature, and will allow powering for future studies.

In a similar study (a parallel study to assess the effectiveness of 200 μg FP per day for 7 days compared to Placebo in patients with allergic rhinitis), clinical response was based upon categorical symptom score (similar to TNSS), and the between subject SD was 0.67 on a log scale. Assuming this estimate of variability is typical of the expected variability in this study, 48 subjects are sufficient to detect a decrease in symptom score of 50% or more at a power of at least 90% assuming a two-sided significance level of 5%.

Final analysis: The primary analysis was comparison of weighted mean (0 to1 hour (h)) of total nasal symptoms score (TNSS) between

Allergen Challenge versus(vs) Placebo Challenge on Day 7

FP+Allergen Challenge vs Placebo Challenge on Day 7

The data was analysed using an analysis of covariance model. Baseline (pre-challenge TNSS, i.e. at 0 h, on Day7) was included in the model as a covariate. An estimate of the treatment comparisons were calculated between the adjusted means (LS means) along with the associated 95% confidence interval (CI).

The weighted mean of the individual symptom scores of nasal blockage, rhinorrhea, nasal itching and sneezing for each of the challenges were also analysed and presented as above.

Mean profile plots showing the mean (and 95% CI when necessary) value by treatment of TNSS and the symptom scores at each time point on Day 7 were also produced. To obtain the estimates for the profile plots over the 0 to 1 h a mixed effects analysis of variance model was used, fitting baseline, time, treatment, baseline*time and time*treatment interaction as fixed effects, with subject as a random effect and time as a repeated effect. Baseline was defined as pre-challenge TNSS, i.e. at 0 h.

For all the statistical models fitted, model and distributional assumptions underlying each analysis was assessed by visual inspection of residual plots. Homogeneity of variance was assessed by plotting the residuals against the predicted values from the model, whilst normality was assessed using normal probability plots.

Cumulative distribution function plots (3 separate plots) and boxplots (one plot) for weighted mean TNSS were produced for each challenge.

The 'All Subjects' population was defined as all subjects who received study medication for 7 days as per protocol and who provided data at day 7. This population was used for all study disposition and safety analyses. No formal analysis of safety data was performed. Following review of the allergen concentration data and after discussion with the site it became apparent that ten subjects had either not been challenged correctly or had received incorrect study medication. It was not possible to confirm which challenge or study medication these subjects received. The pharmacodynamic analyses is based on the Exploratory population where these subjects have been excluded.

Study Population: Male and female subjects were recruited with allergic rhinitis.

Number of Subjects:	**FP + Allergen**	**Placebo + Allergen**	**Placebo + Vehicle**
Planned N	16	16	16
Dosed N	11	11	13
Completed n (%)	11(100)	11(100)	12(92)
Total Number Subjects Withdrawn N (%)	0	0	1(8)

Withdrawn due to Adverse Events n (%)		0	0	0
Withdrawn due to Lack of Efficacy n (%)		0	0	0
Withdrawn for Other Reasons n (%)		0	0	1(8)
Demographics		**FP + Allergen**	**Placebo + Allergen**	**Placebo + Vehicle**
N		11	11	13
Females: Males		6:5	3:8	4:9
Mean Age in Years (sd)		38.5(13.90)	40.4(16.06)	38.3(15.46)
Mean Weight in Kg (sd)		81.95(15.079)	83.74(13.346)	76.66(9.565)
White n (%)		6(55)	11(100)	10(77)
Pharmacodynamics (PD): Summary of statistical analysis of weighted mean (0-1 h) TNSS and its individual components is described the following table, as based on Exploratory Population				
Parameters	**Treatment**	**N**	**n**	**Adjusted mean (SE)**
TNSS	Placebo+ Vehicle	13	7	1.698(1.0639)
	Placebo+ Allergen	11	9	4.146(0.8870)
	FP+ Allergen	11	9	4.596(0.9053)
Nasal blockage score	Placebo+ Vehicle	13	7	0.846(0.4202)
	Placebo+ Allergen	11	9	1.669(0.3705)
	FP+ Allergen	11	9	1.751(0.3705)
Rhinorrhea score	Placebo+ Vehicle	13	7	0.564(0.3046)
	Placebo+ Allergen	11	9	1.283(0.2686)
	FP+ Allergen	11	9	1.083(0.2686)
Nasal itching score	Placebo+ Vehicle	13	7	0.484(0.3184)
	Placebo+ Allergen	11	9	0.647(0.2808)
	FP+ Allergen	11	9	1.013(0.2808)
Sneezing score	Placebo+ Vehicle	13	7	0.046(01851)
	Placebo+ Allergen	11	9	0.494(0.1633)
	FP+ Allergen	11	9	0.614(0.1633)

Summary of statistical analysis of weighted mean TNSS and its components by treatment comparison is described in the following table, as based on Exploratory Population

Parameter	Treatment comparison	Difference	95% CI of Difference
TNSS	Placebo+ allergen Vs Placebo + Vehicle	2.448	-0.476, 5.372
	FP + Allergen Vs Placebo+ Allergen	0.450	-2.159, 3.059
Nasal blockage score	Placebo+ allergen Vs Placebo + Vehicle	0.823	-0.339, 1.985
	FP + Allergen Vs Placebo+ Allergen	0.082	-1.005, 1.169
Rhinorrhea score	Placebo+ allergen Vs Placebo + Vehicle	0.719	-0.123, 1.561
	FP + Allergen Vs Placebo+ Allergen	-0.200	-0.988, 0.588
Nasal itching score	Placebo+ allergen Vs Placebo + Vehicle	0.162	-0.718, 1.043
	FP + Allergen Vs Placebo+ Allergen	0.367	-0.457, 1.190
Sneezing score	Placebo+ allergen Vs Placebo + Vehicle	0.449	-0.063, 0.961
	FP + Allergen Vs Placebo+ Allergen	0.120	-0.359, 0.599

Safety results: Time period for collection of adverse events (AEs) and serious adverse events was from the day of Screening until the last visit of Follow-up.

Adverse Events:	FP + Allergen	Placebo + Allergen	Placebo + Vehicle
N	11	11	13
No. subjects with AEs n (%)	7(64)	8(73)	9(69)
Most Frequent AEs n(%)			
Epistaxis	3(27)	5(45)	8(62)
Increased upper airway secretion	0	0	1(8)
Nasal discomfort	1(9)	0	0
Rhinitis allergic	0	1(9)	0
Headache	1(9)	2(18)	3(23)
Syncope vasovagal	1(9)	1(9)	0
Nasopharyngitis	2(18)	2(18)	3(23)
Influenza	1(9)	0	0
Back pain	1(9)	0	0
Musculoskeletal pain	0	0	1(8)
Pain in extremity	0	0	1(8)
Hangover	0	0	1(8)
Influenza like illness	0	0	1(8)
Seasonal allergy	0	0	2(15)
Food poisoning	1(9)	0	0
Post procedural haemorrhage	0	1(9)	0
Hepatic enzyme increased	1(9)	0	0
Hypercholesterolemia	0	0	1(8)
Epididymal Cyst	1(9)	0	0
Pruritus generalised	0	0	1(8)

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: There were no serious adverse events reported in this study.

Publications: None.