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: IPR110723

Title: An 8 day, randomised, double blind, 3-way crossover trial of repeat doses of intranasal investigational product (IP) and fluticasone propionate in the Vienna Challenge Chamber in subjects with seasonal allergic rhinitis (SAR).

Rationale: In some *in vitro* assays and in clinical use in asthma, agents elevating cyclic AMP and steroids have been shown to have complementary effects. It is hypothesized that a PDE4 inhibitor and a steroid may also have complementary effects in SAR. There is potential for topical corticosteroids to be used in conjunction with other topical anti-inflammatory agents, to provide greater control of symptoms and a faster onset of effect.
The aim of the present study was to evaluate whether co-administration of an anti-inflammatory agent such as IP can impart any additional effect to that of a steroid (Fluticasone propionate, FP) in a model of SAR. Given the intention to investigate the additive effects of IP with FP, rather than establishing effects of individual treatments that have already been documented, a placebo arm was not included in the study.

Phase: IIa

Study Period: 16 Jan 2008 to 26 May 2008

Study Design: This was a randomised, double blind, 3-way cross-over study of repeat doses of intranasal IP and fluticasone propionate.

Centres: One centre in Vienna, Austria.

Indication: Seasonal Allergic Rhinitis

Treatment: The subjects were administered IP, FP and matched placebo as per randomisation schedule using aqueous nasal sprays. Investigational product 0.2% w/w and investigational product matched placebo were administered to subjects using aqueous nasal sprays. Fluticasone propionate 0.5% and FP matched placebo were also administered using aqueous nasal sprays. The details of the treatment administration is presented in the below table.

Treatment	Days 1, Day 2, and Day 8		Days 3 to Day 7	
	Morning	Evening[1]	Morning	Evening
FP + IP	FP 200 μg (2 x 50 μg puffs per nostril) administered 30 min prior to IP 200 μg (1 x 100 μg puff per nostril).	IP 200 μg (1 x 100 μg puff per nostril) only.	FP 100 μg (1 x 50 μg puff per nostril) administered with IP 200 μg (1 x 100 μg puff per nostril).	FP 100 μg (1 x 50 μg puff per nostril) administered with IP 200 μg (1 x 100 μg puff per nostril).
FP placebo (PL_{FP}) + IP	FP placebo (two puffs per nostril) administered 30 min prior to IP 200 μg (1 x 100 μg puff per nostril).	IP 200 μg (1 x 100 μg puff per nostril) only.	FP placebo (one puff per nostril) administered with IP 200 μg (1 x 100 μg puff per nostril).	FP placebo (one puff per nostril) administered with IP 200 μg (1 x 100 μg puff per nostril).
FP + IP placebo (PL_{066})	FP 200 μg (2 x 50 μg puffs per nostril) administered 30 min prior to IP placebo (one puff per nostril).	IP placebo (one puff per nostril) only.	FP 100 μg (1 x 50 μg puff per nostril) administered with IP placebo (one puff per nostril).	FP 100 μg (1 x 50 μg puff per nostril) administered with IP placebo (one puff per nostril).

1. Not applicable to Day 8

Objectives: The primary objective of the study was to investigate effect of repeat intranasal doses of FP alone versus IP + FP on nasal symptoms of allergic rhinitis provoked by spending 4 hours (h) in the Vienna Challenge Chamber (VCC) after morning dosing on Day 2.

Statistical Methods: The sample size calculation was based on the requirement to detect a difference of at least one unit in the primary endpoint weighted mean TNSS (1 to 4 h) between FP alone and IP + FP at the 5% one-sided significance level.
Based on the average estimate of within-subject variance of 2.55, a sample size of 48 subjects were required to provide 90% power detect such a difference. Approximately sixty subjects were planned for to be recruitment to ensure at least 48 evaluable subjects.

The primary analysis was the comparison of weighted mean (1 to 4 h) of TNSS between FP compared with IP + FP on Day 2. The data was analysed using a mixed effects analysis of variance (ANOVA) model adjusting for terms due to period and treatment fitted as fixed effects, with subject fitted as a random effect. An estimate of the treatment comparisons on Day 2 was calculated between the adjusted means (Least Square means) along with the associated 90% confidence intervals (CIs). The distribution of the data of subjects with pre-chamber TNSS was expected to be skewed to zero; therefore baseline was not included in the main analysis.
The secondary analysis was the comparison of weighted mean (1 to 4 h) of all endpoints (TNSS, components of TNSS, eye symptom score, global symptom score, nasal airflow and nasal secretion) between FP alone vs. IP + FP and IP alone vs. IP + FP on Day 2 and Day 8. All these endpoints were analysed in a similar fashion to the primary endpoint.

Study Population: Healthy non-smoking males and females aged 18 to 50 years inclusive, with body weight 55 kg (females 50 kg) to 95 kg inclusive and body mass index (BMI) less than 29.0 kg/m^2. Subjects had history of SAR, exhibited a moderate response to 1500 grass pollen grains /m^3 after 2 h in the VCC (defined nasal symptom score of at least 6). Subjects also had positive skin prick test (wheal ≥4 mm) and RAST (≥ class 2) for grass pollen at or within the twelve months preceding the Screening Visit, forced expiratory volume at 1 second (FEV_1- maximum recorded value) ≥80% of predicted, FEV_1/forced vital capacity (FVC-maximum recorded value) ratio ≥70% predicted. Subjects who met these criteria were included in the study.

Number of Subjects:	Total
Planned N	60
Dosed N	55
Completed n (%)	49 (89)
Total Number Subjects Withdrawn N (%)	6 (11)
Withdrawn due to Adverse Events n (%)	1 (2)
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons (Withdrew consent) n (%)	5 (9)
Demographics	
N	60
Females: Males	22 : 33
Mean Age in Years (Range)	26.9 (19 - 42)
Mean Weight in Kg (Range)	70.63 (50 - 95)
White n (%)	52 (95)

Pharmacodynamics (PD): A summary of the statistical comparisons of all efficacy endpoints is presented in the table below.

Endpoint (Weighted Mean 0-4 h)	LS Means	Differences (vs IP 200 µg BID+ FP)	90% CI of Differences
	FP	FP	FP
TNSS (Day 2)	6.88	-0.38	(-0.87, 0.11)
TNSS (Day 8)	5.39	-0.35	(-0.83, 0.13)
Nasal Blockage (Day 2)	1.80	-0.06	(-0.22, 0.09)
Nasal Blockage (Day 8)	1.44	-0.07	(-0.22, 0.09)
Nasal Itching (Day 2)	1.92	-0.18	(-0.31, -0.05)
Nasal Itching (Day 8)	1.55	-0.14	(-0.27, -0.01)
Rhinorrhea (Day 2)	1.68	-0.03	(-0.17, 0.12)
Rhinorrhea (Day 8)	1.27	0.04	(-0.10, 0.18)
Sneezing (Day 2)	1.48	-0.11	(-0.28, 0.06)
Sneezing (Day 8)	1.12	-0.18	(-0.34, -0.03)
Eye SS (Day 2)	2.16	-0.06	(-0.49, 0.38)
Eye SS (Day 8)	1.76	-0.33	(-0.71, 0.04)
Global SS (Day 2)	10.42	-0.70	(-1.59, 0.19)
Global SS (Day 8)	8.28	-1.02	(-1.78, -0.25)
Nasal Airflow (cm^3/s) (Day 2)	352.05	-2.69	(-26.73, 21.34)
Nasal Airflow (cm^3/s) (Day 8)	389.73	7.92	(-20.12, 35.97)
Nasal Secretion Weight (g) (Day 2)	2.22	-0.23	(-0.69, 0.23)
Nasal Secretion Weight (g) (Day 8)	1.29	-0.49	(-0.79, -0.20)

Safety results: All the AEs occurring from the time a subject consented to participate in the study until completion of the study (including any follow-up period) were recorded. Two events were considered to be severe in intensity by the

Investigator (sneezing and breast pain). The number of subjects reporting AEs is summarised in the table below.	
Adverse Events:	FP
N	52
Any AE n (%)	4 (8)
All AEs n (%):	
Epistaxis	0
Nasal congestion	0
Nasal discomfort	0
Rhinorrhoea	0
Sneezing	1 (2)
Nasopharyngitis	0
Pneumococcal infection	0
Headache	2 (4)
Eye pruritis	1 (2)
Vomiting	0
Breast pain	0
Phlebitis	0
Serious Adverse Events, n (%): There were no deaths or non fatal serious adverse events (SAE) reported during the study.	

Publications: None