**CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A6431079-P**

**Protocol Title:** Perception and tolerability of nicotine films for use in the mouth. A randomized, double-blind, crossover, phase-II, study in healthy smokers.

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**Publications Based on the Study:** None

**Study Initiation and Completion Dates:** 8 March 2005 to 17 March 2005

**Phase of Development:** Phase 2

**Study Objective(s):**

The primary objective was:
to investigate smokers' overall acceptability at 20 minutes after administration of a pullulan-based nicotine film at doses of 2 and 3 mg and a metolose-based nicotine film at 2 mg.

The secondary objectives were:

- to investigate smokers' overall acceptability at 0.5, 2 and 5 minutes after administration of the study products,
- to investigate particular aspects of the acceptability of the study products,
- to determine if any of the study products is more preferred than the others,
- to assess urges to smoke at specified times during the study treatments,
- to assess tolerability and safety of the study treatments.

**Study Design:**

In the present crossover study, the three treatments were administered during one day with an interval of one and a half hour between the treatments. The investigational products, given in randomized order, included pullulan-based films containing 2 and 3 mg nicotine, respectively, and a metolose-based film containing 2 mg nicotine. The acceptability, tolerability and palatability of the study products were investigated. A questionnaire addressing acceptability was completed at 0.5, 2, 5 and 20 minutes after each dose. Safety was assessed continuously throughout the visit. In addition, questions about urges to smoke were included. To improve interpretability of observed relationships, treatment labels of the films were not revealed to subjects or trial personnel.

The primary study endpoint was overall acceptability rated 20 minutes after dose. Secondary endpoints were acceptability at 0.5, 2 and 5 minutes after dose, results on other aspects on acceptability as described in Appendix 1, urges to smoke, preference of study product and the occurrence of adverse events.

**Number of Subjects:**

| | |
|---|---|
| Planned: | 60 |
| Screened: | 153 |
| Assigned to Treatment: | 60 |
| Treated: | 48 (1s was rejected; 11ss withdrew consent before start of study) |
| Completed: | 48 |
| Discontinued: | 0 |
| Evaluated: | 48 |
| Analyzed for Adverse Events: | 48 |

**Diagnosis and Main Criteria for Inclusion:**

Healthy male and female subjects between the ages of 20 and 50 years, inclusive, smoking at least 10 cigarettes daily during at least three years preceding inclusion and no intention to quit within three months from inclusion.

Females had to be in a postmenopausal state with absence of menstrual discharge for at least two years and a serum FSH level >30 IU/L, or premenopausal/perimenopausal state with effective contraception (oral or implanted hormonal contraceptives, intrauterine device or status after operative sterilization).

**Identity and Administration of Treatments:**

| Drug | Form | Appearance | Route | Dose | Regimen | Batch No. |
|---|---|---|---|---|---|---|
| Nicotine pullulan film | Film | Rectangular, green film | Oral | 2 mg | 1 x 2 mg | FLN 1381 |
| Nicotine metolose film | Film | Rectangular, green film | Oral | 2 mg | 1 x 2 mg | FLN 1376 |
| Nicotine pullulan film | Film | Rectangular, green film | Oral | 3 mg | 1 x 3 mg | FLN 1375 |

The subjects were instructed to place the film on the tongue, to let it melt, and to not swallow it before it had melted.

**Pharmacodynamic Evaluations:**

The acceptability, tolerability and palatability of the study products were investigated using questionnaires (cf. Table 5). In addition, product preference and predictability of how the products will work in smoking cessation/reduction were evaluated.

**Safety Evaluations:**

Medical Dictionary for Regulatory Activities (MedDRA) was employed as adverse event classification system. The frequency of subjects experiencing a specific treatment-related adverse event was tabulated by treatment, preferred term, and severity. The number of each type was calculated. Adverse events that were considered treatment-related were listed separately.

**Statistical Methods:**

Acceptability, tolerability and palatability of the study products were evaluated using Likert scales. Results were tabulated for each subject and treatment showing frequency and percentage for each category and treatment. Descriptive statistics showing mean, standard deviation, median, minimum and maximum values for each treatment were tabulated together with 95% confidence intervals of means. Urges to smoke was measured using a 100 mm VAS. Descriptive statistics showing mean, standard deviation, median, minimum and maximum values were tabulated. The question on preference was tabulated showing frequency and percentage for each treatment. The hypothesized multinomial distribution for preferred treatment, asked in conjunction with the last dose, was 1/3 for each of the treatments. The chi-square distribution was used to test if there was a significant departure from the hypothesized distribution.

**Pharmacodynamic Results:**

The table below shows the results for the primary endpoint.

| **Treatment** | **Overall acceptability score 20 minutes after administration (mean±SD) scale: 1 (extremely unacceptable) – 9 (extremely acceptable)** |
|---|---|
| Pullulan 2 mg | 7.5 ± 1.2 |
| Metolose 2 mg | 6.4 ± 2.1 |
| Pullulan 3 mg | 6.7 ± 1.8 |

A majority of the subjects believed that the products would work “moderately” or “very much” for smoking cessation/reduction. All films decreased cigarette craving within minutes after application. The best liked product was pullulan 2 mg.

**Safety Results:**

Most treatment related adverse events were of gastrointestinal and oro-pharyngeal character. The most common AEs were hiccups (12 reports), throat tightness (12 reports) and throat irritation (10 reports).

**Conclusions:**

Although this study did not compare test formulations directly to other NRT products, based on data collected on palatability, acceptability, safety and prediction of clinical effectiveness it is concluded that the test formulations, in particular the pullulan 2 mg film, would be a strong alternative to current NRT products.