CLINICAL STUDY REPORT

NICOTINE; OROMUCOSAL NICOTINE SPRAY

PROTOCOL NUMBER: A6431111

EFFICACY AND SAFETY FOLLOWING USE OF A NOVEL NICOTINE REPLACEMENT THERAPY. A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, 52-WEEK STUDY IN SMOKERS MOTIVATED TO QUIT

Indication Studied:	Smoking Cessation
Developmental Phase of Study:	PHASE 3
Study Initiation Date: (First Subject Enrolled)	27 March 2009
Study Completion Date: (Last Subject Completed)	16 June 2010
Status/Date	Final Version 15 February 2011
Approvers	Hans Lauri, Study Manager, McNeil AB Roland Perfekt, Statistics Manager, McNeil AB Elisabeth Kruse, Director, Global Medical Affairs & Clinical Research, McNeil AB Åke Westin, Associate Director, Biometrics and Clinical Data Systems, McNeil AB Andre Mann, Medical Safety Officer, Smoking Cessation, McNeil Consumer Healthcare

1. SYNOPSIS

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Oromucosal Nicotine Spray ***Name of Active Ingredient:*** Nicotine	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: Efficacy and Safety Following Use of a Novel Nicotine Replacement Therapy. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, 52-Week Study in Smokers Motivated to Quit.

Investigators:

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Study Centers: The study was conducted at 3 investigative centers located in Denmark (1 center) and Germany (2 centers).

Publication (reference): None

Study Period: *Phase of Development:* 3

Date of first enrollment: 27 March 2009

Date of last completed: 16 June 2010

Objectives: The primary objective was to evaluate the efficacy of an Oromucosal Nicotine Spray (ONS) versus placebo in smokers to achieve continuous abstinence from smoking from the Week 2 visit until and including the Week 6, Week 24, and Week 52 visits, respectively.

Secondary objectives were:

To evaluate the efficacy of ONS versus placebo in smokers to achieve continuous abstinence from smoking from the Week 2 visit through all other time points throughout the study (i.e., until and including the Weeks 4, 8, 12, 16, and 20 visits, respectively)

To evaluate the efficacy of ONS versus placebo in smokers on 7-day point prevalence abstinence from smoking at Week 4 and all remaining visits

To assess the efficacy of ONS versus placebo in smokers on craving and withdrawal symptoms during the initial 4 weeks on study (daily ratings), as well as point ratings at Weeks 4, 6, 8, 12, 16, 20, and 24

To document the compliance of ONS

To assess the level of nicotine substitution by measuring saliva cotinine levels

To document smoking status throughout the study

To evaluate the safety and adverse event (AE) profile of ONS, including vital sign measurements

To evaluate the product acceptability of ONS

Methodology: This was a 52-week randomized, multicenter, double blind, placebo-controlled, parallel group study to measure the efficacy and safety of ONS for the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers who were motivated to quit. Participants who were still smoking at the end of the study, either because they failed to quit or resumed smoking, were recommended to contact a standard smoking cessation treatment clinic or their general practitioner.

Preliminary eligibility for the study was checked during a telephone screening; potentially eligible participants were instructed to come to the study center for a baseline visit, during which they were enrolled in the study after satisfying the inclusion and exclusion criteria, including giving written informed consent. Baseline measurements were recorded, and the subjects were then randomly assigned to receive either active or placebo treatment in a 2:1 ratio. Study personnel provided general smoking cessation advice in writing and a brief discussion (< 10 minutes) of this advice to eligible participants. Subjects were then instructed to quit smoking on the next day and to start using the ONS. All subjects were instructed to follow the ONS dispenser directions for use that were provided to them. Subject participation in the study included a 6-week period of full study drug treatment, a 6-week period of tapering study drug treatment, a 12-week period of occasional use, a 30-day safety follow-up period, and a 24-week follow-up period with no study drug treatment. At all visits after the baseline visit, up to and including the Week 24 visit, study personnel discussed smoking cessation advice very briefly (< 3 minutes) with all subjects.

Number of Subjects (planned and analyzed): Planned enrollment: 465 subjects (310 receiving active treatment and 155 receiving placebo)

Analyzed: 479 subjects (318 receiving active treatment and 161 receiving placebo)

Diagnosis and Main Criteria for Inclusion: Adult (18 years or older) male and female subjects who have been daily cigarette smokers for the last 3 years or more with carbon monoxide (CO) levels of at least 10 ppm after at least 15 smoke-free minutes. Subjects must be willing to quit smoking, to use ONS for at least 12 weeks, to comply with all study procedures, and to use an electronic diary (eDiary) according to provided instructions.

Test Product, Dose and Mode of Administration, Batch Number: Oromucosal Nicotine Spray, containing 1 mg of nicotine per metered spray dose, for administration into the oral cavity. Batch numbers: KLN1529, KMN1532, and KMN1533.

Duration of Treatment: Subject participation in the study included a 6-week period of full study drug treatment, a 6-week period of tapering study drug treatment, a 12-week period of occasional use, a 30-day safety follow-up period, and a 24-week follow-up period with no study drug treatment.

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo oromucosal spray for administration into the oral cavity. Batch number: KLN1530.

Criteria for Evaluation:

Primary Efficacy Variable: The primary efficacy variable was the self-reported, CO-verified continuous abstinence from smoking from the Week 2 visit until and including the Weeks 6, 24, and 52 visits, respectively. Treatment success and failure were defined in the protocol (Appendix 16.1.1) and the Statistical Analysis Plan (Appendix 16.1.9) (see also Section 9.7.5.1)

Secondary Efficacy Variables:

Self-reported, CO-verified continuous abstinence from smoking from the Week 2 visit until and including the Weeks 4, 8, 12, 16, and 20 visits

Self-reported, CO-verified 7-day point prevalence abstinence from smoking at Weeks 4, 6, 8, 12, 16, 20, 24, and 52

Craving and withdrawal symptoms, as recorded in the subject eDiary during the initial 4 weeks, and corresponding point ratings at Week 4, 6, 8, 12, 16, 20, and 24

Degree (%) of nicotine substitution for subjects with active treatment as estimated from saliva cotinine measurements at Baseline and at Weeks 2, 6, 12, and 24

Smoking status as reported by the subject at each visit

CO in exhaled air as recorded at all visits except at Week 28 (telephone contact only)

Safety Variables:

The number and percentage of subjects experiencing treatment-emergent AEs, including the following: treatment-related AEs overall, treatment-related AEs with onset during the first 6 weeks of the study, treatment-related AEs with onset on the same day, and

treatment-related AEs by severity

The number and percentage of subjects experiencing new or worsened oral abnormalities/lesions as assessed through visual mouth inspections at Weeks 2, 12, and 24

Vital sign measurements, including systolic and diastolic blood pressure and pulse as recorded at all visits up to Week 24

Other Variables:

The number of ONS doses used, as recorded daily in the subject eDiary throughout the first 12 weeks of the study and as recorded in the CRF at Weeks 16, 20, and 24

Spray usage pattern, i.e., the location in the mouth most frequently used for spray application, as recorded in the CRF at all visits from Week 1 through Week 24

Weight changes (in kg) from Baseline as derived from weight assessments at Baseline and Weeks 6, 12, 16, 20, 24, and 52

Open-ended and ordinal scale ratings on product acceptability as assessed at Weeks 1, 6, and 12

Statistical Methods: All significance tests were 2-sided and performed at the 5% level. All confidence intervals (CIs) were calculated by using normal approximations. No adjustment for multiplicity was made, but *P* values are presented for each test to allow for relevant interpretation. No data imputations were performed.

Baseline and demographic characteristics, as well as all primary and secondary efficacy, safety, and other variables, are presented in tabular format and summarized descriptively, where appropriate. Descriptive statistics are mean, standard deviation, median, minimum, and maximum for continuous variables and frequency and percentage for categorical variables.

The primary efficacy analysis was based on subjects in the Full Analysis Set (FAS), which included all randomly assigned study subjects who received study treatment. The statistical evaluation of the primary variables, i.e., self-reported CO-verified statements of continuous smoking abstinence from Week 2 until and including the Weeks 6, 24, and 52 visits, respectively, was performed in a hierarchical order starting with the outcome at the Week 6 visit. Specific definitions of treatment success and failure were developed and are described in the Statistical Analysis Plan.

Safety Analyses: Safety analyses were based on the Safety Analysis Set (identical to the FAS). The number and percentage of subjects experiencing AEs was tabulated by treatment, system organ class, and preferred term. In addition, subjects with AEs that were considered treatment-related were tabulated separately by treatment, system organ class, preferred term, and severity. All SAEs were listed separately.

SUMMARY - CONCLUSIONS

Efficacy Results: The primary efficacy variables were the self-reported, CO-verified continuous abstinence from smoking from the Week 2 visit until and including the Weeks 6, 24, and 52 visits, respectively. Subjects receiving active treatment had statistically significantly higher continuous abstinence rates at Weeks 6, 24, and 52 ($P = 0.014$, 0.006, and 0.007, respectively) compared with those for subjects receiving

placebo. Based upon the hierarchical test procedure applied, it can be concluded that, at a significance level of 5%, the abstinence rates were higher for the active treatment group compared with those for the placebo group at all 3 assessment time points.

The difference between treatments in CO-verified continuous abstinence from Week 2 to Weeks 4, 8, 12, 16, and 20 between subjects receiving active treatment and those receiving placebo was statistically significant at all time points except for Week 12. The highest abstinence rates were observed for the active treatment group at all assessment time points.

The difference in CO-verified self-reported 7-day point prevalence abstinence from smoking at Weeks 4, 6, 8, 12, 16, 20, 24, and 52 between subjects receiving active treatment and those receiving placebo was statistically significant and favored active treatment at all assessment time points.

Subjects with CO-verified 7-day point prevalence abstinence exhibited a steep rate of decrease in median cotinine levels. Median percent cotinine substitution values dropped from 37.0% at Week 2 to 1.0% at Week 24. As expected, subjects in the FAS showed decreases in median cotinine levels and median percent cotinine substitution values that were much less than those for the abstinent subjects.

Overall, decreases in mean rating scores for the desire/urge to smoke (craving for cigarettes) were reported by abstinent subjects in both groups from Week 1 through Week 24. Through Week 8, the mean scores of subjects in the active treatment group were lower than those of subjects in the placebo group; as expected from results of previous studies, the difference was statistically significant at Weeks 1 and 2, but not at subsequent visits. There were no remarkable differences between placebo and active treatment in the withdrawal symptoms of Anxiety, Depressed Mood, and Increased Appetite. Statistically significant differences in favor of active treatment were seen at some time points (within the first 6 weeks of treatment) in the mean scores for Irritability/Frustration/Anger, Restlessness, Difficulty Concentrating, and Difficulty Sleeping. Mean values of the aggregated withdrawal score, summing up all the seven separate withdrawal symptom scores, show decrease over time among reporting abstinent subjects as well as lower values for the active treatment group compared to placebo up to and including the visit at 12 weeks (statistically significant for weeks 1, 3, and 4, while the p-value week 2 was 0.054).

Subjects who reported the highest number of cigarettes smoked per day at Baseline showed the most frequent use of ONS, indicating subject understanding of the dosing instructions. For subjects in the FAS, the median daily number of spray doses was higher in the placebo group than that in the active treatment group through Week 3 and similar for both groups thereafter. During Weeks 16 through 24, spray usage decreased in both groups, but lower percentages of subjects receiving placebo generally reported daily use than did subjects receiving active treatment.

The most common location in the mouth toward which the ONS was directed was straight into the mouth.

The overall product rating was high in both groups for subjects in the FAS. In general, subjects receiving the active treatment found the ONS to be moderately to very effective in relieving their cravings quickly and very convenient to use. Product acceptability ratings were generally higher among the group of subjects who were continuously abstinent from smoking.

Safety Results: During the first 12 weeks of treatment, subjects were asked to report any AEs daily in the eDiary prompted by a checklist of 14 specified AEs or they could choose

"Other" and report details at the study visits. After the Week 12 visit, AEs were reported at the study visits only. This may explain the relatively high incidence of AE reports for both active and placebo treatment groups compared with other studies.

The ONS was generally well tolerated and no safety issues were identified. Overall, 88.7% of subjects reported at least 1 AE; the percentage of subjects reporting AEs was somewhat higher in the active treatment group than in the placebo group (91.8% vs 82.6%, respectively).

Treatment-related AEs were reported by 82.0% of subjects; again, the percentage of subjects reporting AEs was somewhat higher in the active treatment group than in the placebo group (87.4% vs 71.4%, respectively). The treatment-related AEs reported by at least 10% of subjects in the active treatment group were hiccups, throat irritation, headache, nausea, dyspepsia, stomatitis, salivary hypersecretion, dizziness, constipation, dry mouth, dysgeusia, and burning sensation. Relatively more subjects in the active treatment group reported treatment-related AEs than did subjects in the placebo group regardless of gender or age group (ie, 18 to 39 years, 40 to 54 years, and 55 years and older).

The percentage of subjects with worst-case severity rating mild or moderate for treatment-related AEs was in both cases similar between the two treatment groups. However, the percentage of subjects with at least one severe treatment-related AE was more than 2.5 times greater for subjects in the active treatment group (19.8%) compared with those in the placebo group (7.5%).

The incidence of eDiary reported AEs declined over the 12 weeks the eDiary was used. For example, during the first week 32% of subjects in the active treatment group reported at least one hiccup in the eDiary. Corresponding figures among reporting active subjects for weeks 6 and 12 were 20% and 7%, respectively.

One death was reported during the study. SAEs were reported by 5.0% of subjects in both treatment groups. Neither the death nor any of the SAEs were judged by the investigator to be related to the study medication. Discontinuation from study due to AEs was reported by 8.6% of subjects; rates were similar between the treatment groups (9.1% in the active treatment group and 7.5% in the placebo group).

Treatment related blood pressure findings (reported preferred term: blood pressure increased, diastolic hypertension or hypertension) were reported by 2.5% of subjects in the active treatment group and by 0.6% in the placebo group. There were no severe events among the treatment related blood pressure findings.

Mean increases in body weights were seen in both treatment groups in the FAS as well as in the subgroup of subjects who were verified as continuously abstinent from Week 2. The increases were similar between treatment groups.

Results from the visual mouth inspection showed that no subjects had worsened abnormalities or lesions during the study period. One or more new oral abnormalities or lesions were reported for 7 subjects (4.3%) in the placebo group and 18 subjects (5.7%) in the active treatment group. There were no abnormalities or lesions that were rated as severe; most events were rated as mild.

Conclusions: The primary objective of this study was to evaluate the efficacy of ONS versus placebo in smokers to achieve continuous abstinence from smoking from the Week 2 visit until and including the Week 6, Week 24, and Week 52 visits, respectively. Subjects receiving active treatment had statistically significantly higher continuous

abstinence rates at Weeks 6, 24, and 52 (P = 0.014, 0.006, and 0.007, respectively) compared with those for subjects receiving placebo. Based upon the hierarchical test procedure applied, it can be concluded that, at a significance level of 5%, the abstinence rates were higher for the active treatment group compared with those for the placebo group at all 3 assessment time points. Even at Week 52 after 24 weeks with no ONS treatment, the percentage of subjects who had received active treatment and remained abstinent (13.8%) was nearly 2.5 times greater than that of subjects who had received placebo (5.6%). Risk ratios for success with active treatment compared with placebo or no treatment were 1.6, 2.3, and 2.5 at Weeks 6, 24, and 52, respectively.

The rates of CO-verified continuous abstinence from the Week 2 visit through all other time points throughout the study (ie, until and including the Weeks 4, 8, 12, 16, and 20 visits, respectively) were also statistically significantly higher for subjects receiving active treatment compared with those receiving placebo at all time points except for Week 12 (P=0.055).

Likewise, the active treatment showed improved efficacy versus placebo in smokers on 7-day point prevalence abstinence from smoking at Week 4 and all remaining visits; the difference between subjects receiving active treatment and those receiving placebo was statistically significant at all assessment time points.

Statistically significant differences between active treatment and placebo were seen at several time points within the first 6 weeks of treatment in the rating scores for desire/urge to smoke (cravings) and 4 of the 7 withdrawal symptoms evaluated. Likewise, the aggregated withdrawal score were statistically significant in favor of the active treatment for weeks 1, 3, and 4 (while the p-value week 2 was 0.054).

Subjects who reported the highest number of cigarettes smoked per day at Baseline showed the most frequent use of ONS, indicating subject understanding of the dosing instructions. Overall, approximately two-thirds to three-quarters of these subjects reported using fewer than the recommended doses during Weeks 1 through 6. The percentage of subjects reporting spray usage that was greater than the recommended doses was generally less than 5%.

Overall, the ONS was well tolerated and no safety issues were identified. The most common treatment-related AEs reported by subjects in the active treatment group were hiccups, throat irritation, headache, nausea, dyspepsia, stomatitis, salivary hypersecretion, dizziness, constipation, dry mouth, dysgeusia, and burning sensation. There were no remarkable trends noted for vital sign measurements.

The overall product rating was high in both groups for subjects in the FAS. In general, subjects receiving the active treatment found the ONS to be moderately to very effective in relieving their cravings quickly and very convenient to use. Product acceptability ratings were generally higher among the group of subjects who were continuously abstinent from smoking.

Overall, the ONS demonstrated good treatment efficacy that met expectations and was similar to results from previous studies of NRTs in similar settings. The product was well tolerated and no unexpected safety signals were identified.

Date of the Report: 15 February 2011