NICOTINE, NICORETTE®

NICTDP2010

PILOT STUDY ON USAGE PATTERNS OF A NOVEL NICOTINE REPLACEMENT THERAPY - A MULTI-CENTER, OPEN, 3-WEEK, RANDOMIZED, LOW-INTERVENTION STUDY OF TWO DIFFERENT DIRECTIONS FOR USE IN SMOKERS MOTIVATED TO QUIT.

Indication Studied:	Smoking cessation
Developmental Phase of Study:	2
Study Initiation Date (First Subject Enrolled):	September 13 2008
Study Completion Date (Last Subject Completed):	December 12 2008
Status/Date:	Final 27 May 2009 Revised 12 Nov 2009
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2. SYNOPSIS

TITLE OF STUDY:

Pilot study on usage patterns of a novel nicotine replacement therapy - A multi-center, open, 3-week, randomized, low-intervention study of two different directions for use in smokers motivated to quit.

PROTOCOL NUMBER: NICTDP2010

INVESTIGATORS:

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STUDY CENTER(S):

University of Birmingham and Tobacco Dependence Research Centre, London, UK

PUBLICATIONS (REFERENCE): NONE

STUDY INITIATION AND COMPLETION DATES:

Date of first subject enrollment: September 13 2008

Date of last subject completed: December 12 2008

PHASE OF DEVELOPMENT: PHASE 2

STUDY OBJECTIVE(S):

Primary: To investigate and evaluate subjects' usage patterns of nicotine mouth spray (NMS) during a three-week period, when subjects were given either fixed or flexible directions for use of the treatment for smoking cessation. Specifically, mean hourly and daily spray consumption, and maximum usage during specified time intervals, were examined. These were evaluated separately for subjects who did, and did not, meet the criteria for continuous abstinence, respectively.

Secondary objectives:

For continuous abstainers:

- To evaluate craving and withdrawal symptoms during three weeks of use of NMS.
- To assess the level of nicotine substitution by measuring saliva cotinine levels at baseline visit and week 3

For all subjects:

- To evaluate self-reported carbon monoxide (CO)-verified continuous abstinence at week 3
- To evaluate the acceptability of NMS at week 3, and
- To evaluate the safety and adverse event (AE) profile of NMS.

METHODOLOGY AND STUDY DESIGN

A pilot, multi-center, open, 3-week, randomized, low intervention study of two different directions for use of a novel NMS, in 252 healthy smokers motivated to quit smoking. The study comprised 3 weeks of treatment with study drug, plus 30 days' safety follow-up after the end of treatment.

Enrolled subjects were randomized into two groups, that received either fixed or flexible dosage directions for use of the NMS:

- **Fixed-dose regimen**: Subjects were instructed to stop smoking completely, then to use 1-2 sprays of the NMS every 30 minutes to 1 hour.
- **Flexible-dose regimen**: Subjects were instructed to stop smoking completely, then to use 1 spray of the NMS whenever they would normally have smoked a cigarette, or whenever they experienced cravings to smoke.

Subjects in both groups were instructed to commence treatment with one spray per dose, but if this did not reduce their cravings within a few minutes they were instructed to use a second spray.

Subjects recorded spray usage in electronic diaries. At the end of the study, mean hourly and daily use of the spray, and maximum usage during specified time intervals, were examined.

At week 3, abstinence from smoking was evaluated, using subjects' self-reported continuous abstinence from smoking from day after baseline until week 3, verified by an exhaled CO level of less than 10 parts per million (ppm). Subjects also recorded smoking status in the electronic diaries, something which was included in the complete evaluation of continuous abstinence from smoking from day after baseline until week 3.

Safety was evaluated by AEs reported during the study.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):

Planned: 252 subjects (126 in each dosage instruction group)

Analyzed: 258 subjects (129 in each dosage instruction group)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Healthy male and female adult smokers aged 18 years or older who had smoked daily for the previous three years or more, with an expired CO level of at least 10 ppm after at least 15 smoke-free minutes, who were motivated and willing to stop smoking, and were willing to use the NMS for the first 3 weeks of their quit attempt. All subjects were willing and able to

comply with study procedures, including daily use of an electronic diary, and had read and signed an Informed Consent form.

Subjects were excluded from the study if they: were using tobacco-containing products, other than cigarette (e.g., snuff/snus, chewing tobacco, cigars, or pipe); were using other NRT, bupropion, or varenicline, or had undergone any treatment for tobacco dependence during the previous 3 months; had unstable angina pectoris or myocardial infarction during the previous 3 months; were pregnant, lactating or intended to become pregnant; were suspected of alcohol or drug abuse; had participated in other clinical trials within the previous 3 months; or had any important concurrent medical conditions.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Nicotine mouth spray for administration into the oral cavity, which delivers a metered dose of 1 mg of nicotine per spray dose.

Batch number: KEN1513

DURATION OF TREATMENT: 3 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Not applicable. All subjects were treated with the same product.

CRITERIA FOR EVALUATION:

Primary variables:

- Mean hourly and daily number of doses of spray used during weeks 1, 2, and 3, as well as throughout the study,
- Maximum number of doses of spray used during any 30-minute, 1-hour and 24-hour time period.

Secondary variables:

- Mean number of spray use occasions per day during weeks 1, 2, and 3, as well as throughout the study (where one ‘occasion’ is defined as a maximal consecutive number of administered sprays, with a maximum of 5 minutes between any two sprays),
- Ratings of craving/urge to smoke and withdrawal symptoms recorded in subject electronic diaries
- Saliva cotinine levels at baseline and week 3 (in abstinent subjects)
- Self-reported continuous abstinence from smoking from day after baseline until week 3, verified by an exhaled CO level of less than 10 ppm at week 3,
- Product acceptability
- Safety (number and severity of reported AEs).

SAFETY EVALUATIONS:

Number of subjects reporting adverse events and severity of AEs reported.

STATISTICAL METHODS:

The primary analysis was intent-to-treat (ITT), on all study subjects who received at least one dose of study treatment and for whom any data were available. No statistical hypothesis tests were performed.. No data imputations were performed.

Summary statistics were calculated for both primary and secondary endpoint variables, and presented by directions of use category and, where applicable, by continuous 3-week abstinence status. Means, medians, standard deviations and ranges were calculated for continuous variables, and frequency distributions for categorical variables.

OVERALL RESULTS

Overall, usage of NMS was lower than recommended in both the fixed-dosage and flexible-dosage groups. In addition, real-time data registration in eDiaries was poor. These factors make it difficult to analyze detailed use patterns or to draw conclusions regarding some of the primary endpoints (mean hourly number of spray doses used and maximum number of spray doses used within any 30 minutes or 1 hour). On the other hand, daily and weekly based data are reliable. The former has been verified by drug accountability data.

Usage of NMS was initially higher with fixed-dosage instructions than with flexible-dosage instruction, but the difference between the two groups leveled out within the 3-week treatment period. The broadly similar findings in the different dosage groups suggest that the flexible-dosage instruction does not result in significantly lower treatment usage than the fixed-dosage instruction.

Analysis of cotinine levels in the 40 subjects who were continuously abstinent at Week 3 showed that NMS attained a mean nicotine substitution level of approximately 50%. The median substitution was approximately 25%.

No significant differences were observed regarding relief of craving or other withdrawal symptoms between the fixed-dosage and flexible-dosage regimens.

Product acceptability ratings were high overall, with high ratings for speed of action, fresh sensation, and convenience of use. Product acceptability ratings were particularly high among the group of subjects who were continuously abstinent from smoking.

PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER RESULTS:

Not Applicable

SAFETY RESULTS

The NMS was well tolerated during use and no safety issues were identified. Overall, 91.4% of subjects reported at least one AE; the incidence of AEs was slightly lower, but not significantly so, in the fixed-dosage group than the flexible-dosage group (89.8% vs 93.0%, respectively).

Treatment-related AEs were reported by 86.3% of subjects; event rates were similar in the fixed-dosage and flexible-dosage groups (85.9% vs 86.7%, respectively). The most common treatment-related AEs were gastro-intestinal (dry mouth, dyspepsia, nausea, salivary hypersecretion, stomatitis), burning sensation, dizziness, dysgeusia, headache, hiccups, and throat irritation. The types of AEs reported with NMS are well-documented with other oral NRT formulations, such as nicotine chewing gum or nicotine oral inhaler.

There was a slightly higher frequency of reported AE's with increased number of doses taken, and those who reported using the spray above the maximum recommended dose reported more incidences of headache, dizziness and dyspepsia compared to those who used according dose recommendation or below. However, the number of reported AE's even in this high-user group was relatively low and on an acceptable level. It should also be noted that the number of subjects using the spray above the maximum recommended level were very few.

No deaths occurred during the study, and no treatment-related SAEs (5 SAE´s in all) were reported. One subject withdrew from the study due to a treatment-related AE (severe hiccups).

CONCLUSION:

The primary objective of this study was to investigate and evaluate subjects' usage patterns of NMS during a three-week period, when subjects were given either fixed or flexible directions for use of the nicotine mouth spray for smoking cessation. Specifically, mean hourly and daily spray consumption, and maximum usage during specified time intervals, were examined. These were evaluated separately for subjects who did, and did not, meet the criteria for continuous abstinence, respectively.

Usage pattern was assessed through an electronic diary in which participants were told to register all doses right after dosing. Any unregistered real-time doses could be registered at the end of each day, and an additional opportunity was to report unregistered doses at the 3-week visit. The compliance with the electronic diary was overall good, but there was a significant amount of doses that were not reported in real-time. This fact makes it difficult to assess usage patterns over the shorter time intervals, but the registrations per day gives a reasonably good basis for evaluation.

Participants smoked a mean of about 22 cigarettes per day at baseline indicating a recommended dose of about 20 to 45 spray doses per day. The median dose was about a third of the recommended dose. There are a couple of possible explanations for this; a large part of participants smoked already on the first day after baseline, indicating a poor motivation to quit smoking, maybe because they knew they would only be provided study drug for three weeks. Eighty percent of participants had used NRT previously and obviously failed to quit.

Two different dosage instructions were tested in this pilot study, a fixed and a flexible. The main difference between the two was that subjects in receiving the fixed instruction were supposed to use the product on a regular basis, whereas those in the flexible instruction group should use the spray when they would normally smoke a cigarette. During the initial week those in the fixed instruction group used somewhat more doses, but this leveled out over the next two weeks of the study.

The nicotine mouth spray was well tolerated and only one subject withdrew from the study due to adverse events occurring. This case was a male who used a total of 2 sprays and experienced severe hiccups. Five serious adverse events were reported, but none of them were assessed as related to study medication.

Participants rated the nicotine mouth spray highly in most of the acceptability assessments performed. They found the dispenser easy to use and the perceived craving relief was rated high. The major concern overall was the strength of the taste of the product, but the variation of answers was large.

The flexible dose instruction is a new way of dosing nicotine replacement therapy, and one of the aims of this study was to compare this novel dose instruction with a traditional fixed dosing schedule. No major differences were found with regards to incidence of adverse events or relief of withdrawal symptoms between the two instructions. The flexible instruction is intuitive and based on the exact number of cigarettes smoked rather than a dichotomous classification of smokers as either high or low dependent. It is therefore believed this instruction will suit a broader population of smokers.

REVISED REPORT DATE: 12 NOVEMBER 2009