

## **NICOTINE NICTDP2011**

### **NICOTINE PHARMACODYNAMICS WITH A NEW ORAL NICOTINE REPLACEMENT PRODUCT AND NIQUITIN™ LOZENGE. A STUDY IN HEALTHY SMOKERS.**

<b>Indication Studied:</b>	For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit.
<b>Developmental Phase of Study:</b>	2
<b>Study Initiation Date (First Subject Enrolled):</b>	01 February 2010
<b>Study Completion Date (Last Subject Completed):</b>	19 May 2010
<b>Status/Date:</b>	FINAL 05 October 2010 Revised 14 February 2011
<b>Responsible Medical Officer:</b>	Holger Kraiczi, MD, PhD +46 46 19 06 13 +46 46 14 29 17

## 2. SYNOPSIS

**Investigator:** Holger Kraiczi

**Study center(s):** McNeil AB, Department of Clinical Pharmacology, Karl XII gatan 5, SE-222 20 Lund, Sweden

**Publications (reference):** None

**STUDY INITIATION AND COMPLETION DATES:** 01 February 2010 to 19 May 2010

**Phase of Development:** Phase 2

**STUDY OBJECTIVE(S):** The primary objectives of this study were:

- to compare ONS (two sprays of 1 mg nicotine) and NiQuitin™ lozenge 2 mg after 5 hours of witnessed abstinence with respect to urges to smoke during the first 5 minutes after start of treatment,
- to compare ONS (two sprays of 1 mg nicotine) and NiQuitin™ lozenge 4 mg after 5 hours of witnessed abstinence with respect to urges to smoke during the first 5 minutes after start of treatment.

Secondary objectives were:

- to compare the study treatments with respect to the time to a 25%, 50%, 75%, and 90% reduction of the baseline urges to smoke score,
- to compare the proportion of subjects reaching 25%, 50%, 75%, and 90% reduction of the baseline urges to smoke within 1, 3, 5, and 10 minutes for the study treatments,
- to describe the urges to smoke profile of the study treatments during 2 hours after dose,
- to evaluate acceptability of the study treatments,
- to evaluate tolerability and safety of the study treatments.

### **Methodology**

**STUDY DESIGN:** Two doses of each treatment (Table S1), one in the morning and one in the afternoon, i.e., 5 hours after the first administration, were given on three separate treatment visits. On three separate treatment days, all subjects were given two consecutive sprays of ONS 1 mg, one NiQuitin™ lozenge 2 mg, and one NiQuitin™ lozenge 4 mg, respectively. Periods without NRT, each lasting for at least 36 hours, separated the treatment visits.

The subjects abstained from smoking from 8 pm in the evening before each treatment visit until the end of the visit. They came to the study site in the morning of the study days. Following instructions from the study personnel, study treatments were administered by the subjects themselves, in the morning and in the afternoon, 5 hours after the first administration.

Urges to smoke were scored on a 100 mm visual analogue scale repeatedly during the first 2 hours, then once hourly for the following hours. The administration in the morning and the following urges to smoke measurements were performed to allow the subjects to get used to the study products and measurements (training session). At 5 hours after start of the morning administration, study treatment was administered again and urges to smoke were rated frequently for 2 hours. Subjects were also monitored to capture any adverse events that might occur. At the end of the visit a questionnaire on product acceptability was filled in by the subjects.

The subjects were randomly allocated in equal proportions to one of 6 treatment sequences, according to Table 4.

Subjects, study personnel and monitor were aware of whether ONS or lozenge was administered at a given visit. However, the strength of NiQuitin<sup>TM</sup> lozenge was unknown.

**Table S1: Study Treatments**

Treatment	Drug	Form	Route	Nicotine Dose	#Subjects
A	ONS	Oromucosal spray	Oromucosal	2 mg	200
B	NiQuitin™ lozenge	Lozenge	Oromucosal	2 mg	
C	NiQuitin™ lozenge	Lozenge	Oromucosal	4 mg	
Duration of Treatment Periods: 7 hours			Period without NRT between treatment visits: ≥ 36 hours		

**NUMBER OF SUBJECTS (PLANNED AND ANALYZED):** Two hundred (200) subjects were planned and included in the study. Between 186 and 189 subjects per treatment were analyzed with regards to pharmacodynamics and 189-192 with regards to safety.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Healthy male and female subjects between the ages of 19 and 55 years, inclusive, smoking at least 10 cigarettes daily during at least one year preceding inclusion and within 30 minutes of waking up were enrolled. The subjects had to have a Body Mass Index (BMI) between 17.5 and 32.0 kg/m<sup>2</sup> and a total body weight ≥50 kg. Females had to be in a postmenopausal state or in a premenopausal/perimenopausal state with effective contraception (oral, injected or implanted hormonal contraceptives, intrauterine devices or status after operative sterilization).

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

**Table S2: Investigational Products and Identity**

Investigational Product	Vendor Lot ID / Batch Number	Formula Number
ONS	LHN1548	N/A
NiQuitin™ lozenge 2 mg	2019706	N/A
NiQuitin™ lozenge 4 mg	2020005	N/A

Following a 12-hour nicotine abstinence period, subjects received study medication (Table S2), in the morning and then again after 5 hours, that is, at a given visit day, two doses of either 2 consecutive sprays of ONS 1 mg or of one NiQuitin™ lozenge 2 mg or of one NiQuitin™ lozenge 4 mg were administered.

ONS administration: After appropriate instruction by the study personnel, subjects self-administered the spray, i.e., delivered two consecutive sprays of ONS into the mouth. Subjects were advised to avoid swallowing immediately after administration.

NiQuitin™ lozenge 2 mg and 4 mg: Subjects were instructed to place the lozenge in the mouth and to occasionally move the lozenge from one side of the mouth to the other until the lozenge was completely dissolved. Subjects were instructed to not chew or swallow the lozenge.

**DURATION OF TREATMENT:** For 179 of the subjects there were no discrepancies between the randomization schedule and the actual dosing schedule. Further 21 subjects did not complete all treatments and thus received lower doses of nicotine than specified in the protocol.

**Reference therapy, dose and mode of administration, batch number:**

N/A

**Criteria for evaluation:**

All randomized subjects with valid pharmacodynamic (PD) parameter values and without major protocol deviations were included in the evaluation.

All subjects who received at least one dose of treatment were included in the safety analysis set.

**EFFICACY EVALUATION: NO EVALUATION OF EFFICACY WAS MADE.**

**PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER EVALUATIONS**

The following activities were completed:

The momentary intensity of urges to smoke was measured by means of a 100 mm visual analog scale (VAS). On the scale, 0 corresponded to “no urges to smoke” and 100 mm corresponded to “extreme urges to smoke”. Urges to smoke were rated 10, 6, and 2 minutes

prior to and at 1, 3, 5, 10, 15, 20, 25, 30, and 45 min and at 1, 1.5, 2, 3, and 4 hours after start of the morning administration. Urges to smoke were rated at 10, 6, and 2 minutes prior to and at 1, 3, 5, 10, 15, 20, 25, 30, and 45 min and at 1, 1.5, and 2 hours following the afternoon administration. A questionnaire regarding the experienced acceptability of the study product was filled in by subjects at the end of each visit.

**SAFETY EVALUATIONS:** Female subjects of childbearing potential were tested for beta-human chorionic gonadotropin ( $\beta$ -hCG) at screening and before each treatment session.

The investigator obtained and recorded on the CRF all observed or volunteered adverse events, the severity (mild, moderate, severe) of the events, and the investigator's opinion of the relationship to the study treatment. AEs included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator recorded as adverse events any clinically significant changes in physical examination findings and abnormal objective test findings.

### **Statistical methods:**

#### **Analysis of Pharmacodynamic Parameters**

The statistical methodology and procedures described for the analysis of pharmacodynamic parameters pertain to data collected after five hours of witnessed abstinence at the clinic only.

Pair-wise treatment comparisons with respect to  $AUC_{nmin}$ ,  $n = 1, 3, 5$ , and 10, i.e. the area under the linearly interpolated urges-to-smoke-vs.-time curve from time zero (baseline) until  $n$  minutes, were based on a mixed linear model including sequence, treatment, period and baseline urges-to-smoke score as fixed effects, and subject, nested within sequence, as random effect. To avoid inflation of the significance level due to multiple testing, the statistical evaluation of the area under the urges-to-smoke-vs.-time curve from time zero to 5 minutes ( $AUC_{5min}$ ), 3 minutes ( $AUC_{3min}$ ), and 1 minute ( $AUC_{1min}$ ), respectively, was performed in a hierarchical order starting with the 5 minutes' evaluation. Since the primary study objective included two different treatment comparisons the corresponding test significance level was adjusted to 2.5% to insure the overall Type-I error rate was at most 5%.

The distributions of the estimated time to 25%, 50%, 75%, and 90% reduction, respectively, of baseline urges-to-smoke scores were summarized for each treatment using Kaplan-Meier estimation together with estimated 25%, 50%, and 75% quartiles of the survival distributions and corresponding 95% CIs wherever possible. Pair-wise treatment comparisons of the time to 25%, 50%, 75%, and 90% reduction, respectively, of baseline urges-to-smoke scores, were based on the Sign test.

The proportion of subjects reaching 25%, 50%, 75%, and 90% reduction of the baseline urges to smoke within 1, 3, 5, and 10 minutes, respectively, were compared between treatments with the McNemar test.

## Safety Parameters

All adverse events reported during the Adverse Event reporting period were listed by subject ID and last treatment administered at or before Adverse Event onset date. The frequency of subjects experiencing adverse events was tabulated by system organ class, treatment, and preferred term. In addition, adverse events that were considered treatment-related were separately tabulated by treatment, system organ class, preferred term name, and severity. Medical Dictionary for Regulatory Activities (MedDRA) was used as Adverse Event classification system.

## RESULTS

### SUBJECT DISPOSITION AND DEMOGRAPHY:

[Table S3](#) gives the subject disposition and the number of subjects analyzed for PD. All included subjects were analyzed for safety.

**Table S3: Subjects Included in the PD Analyses.**

Treatment	Analyzed for Safety	Analyzed for PD
ONS 2 mg (2 consecutive sprays)	190	186
NiQuitin™ lozenge 2 mg	192	189
NiQuitin™ lozenge 4 mg	189	188

Two hundred (200) subjects, 105 males and 95 females, were included in the study. One hundred and ninety-three (193) subjects were white, five (5) were black, one (1) was Asian and one (1) was of other origin. The subjects were smokers consuming an average of 17.7 cigarettes per day (range 10-50 cigarettes) and had been smokers for 16.8 years on average (range 1-45 years). All subjects smoked within 30 minutes of waking up. Their average age was 32.9 years (range 19-55 years), and their average BMI was 24.1 kg/m<sup>2</sup> (range 18.4-31.8 kg/m<sup>2</sup>). Thus, smoking habits, age and BMI were in accordance with the inclusion criteria.

All subjects were considered healthy adult volunteers at screening, i.e., none of them had conditions or a medical history that the investigator considered sufficient to affect the conduct or validity of the study or to represent a potential risk to the subject during study participation.

### EFFICACY RESULTS: NO EFFICACY EVALUATION WAS PERFORMED.

### Pharmacokinetic, Pharmacodynamic, and/or Other Results:

#### Pharmacodynamic Results

Figure S1 displays the average urges to smoke vs. time profiles over 2 hours after the afternoon dose. Table S4 shows the areas under the urges-to-smoke-vs.-time curves and comparisons between treatments. Figure S2 and Figure S3 show the proportion of subjects

attaining 25%, 50%, 75%, and 90% reduction of baseline craving scores by treatment and time since start of treatment.

Table S5 shows estimated median times to 25% and 50% reduction of baseline urges to smoke scores.

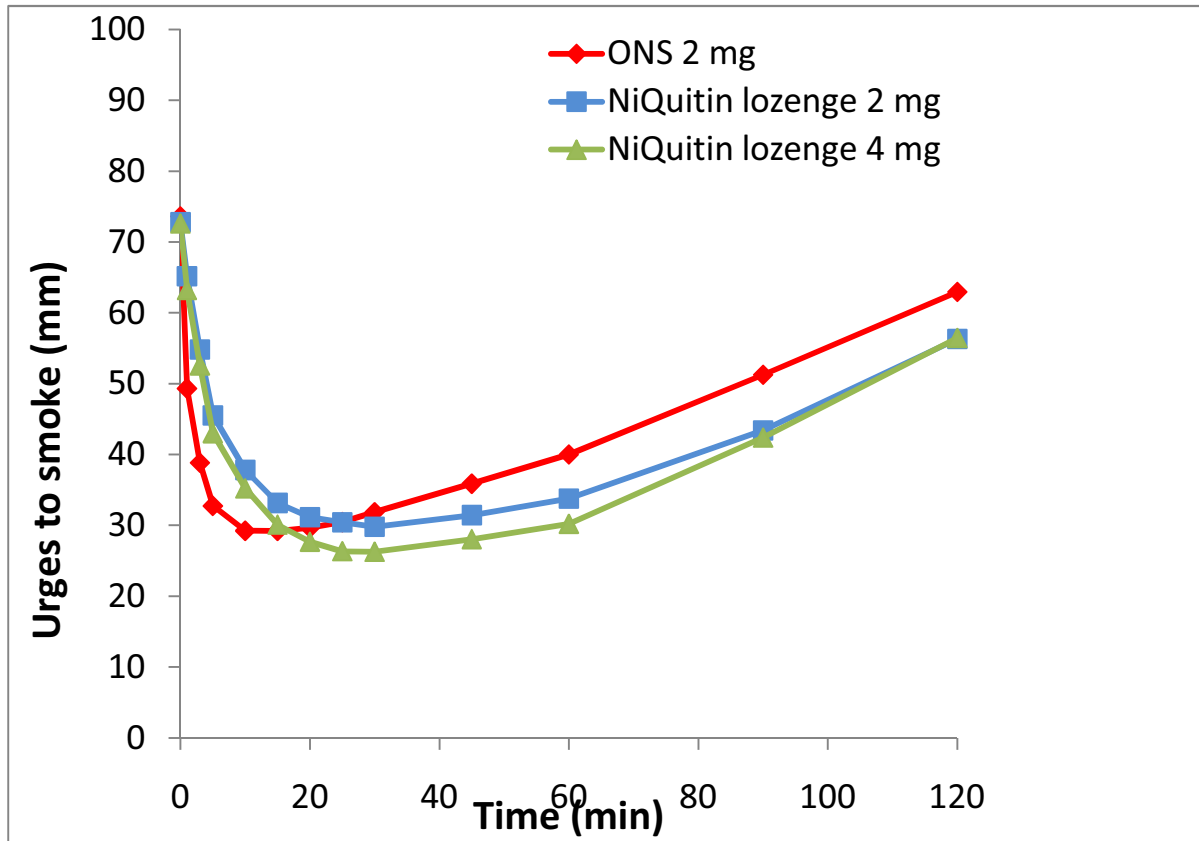


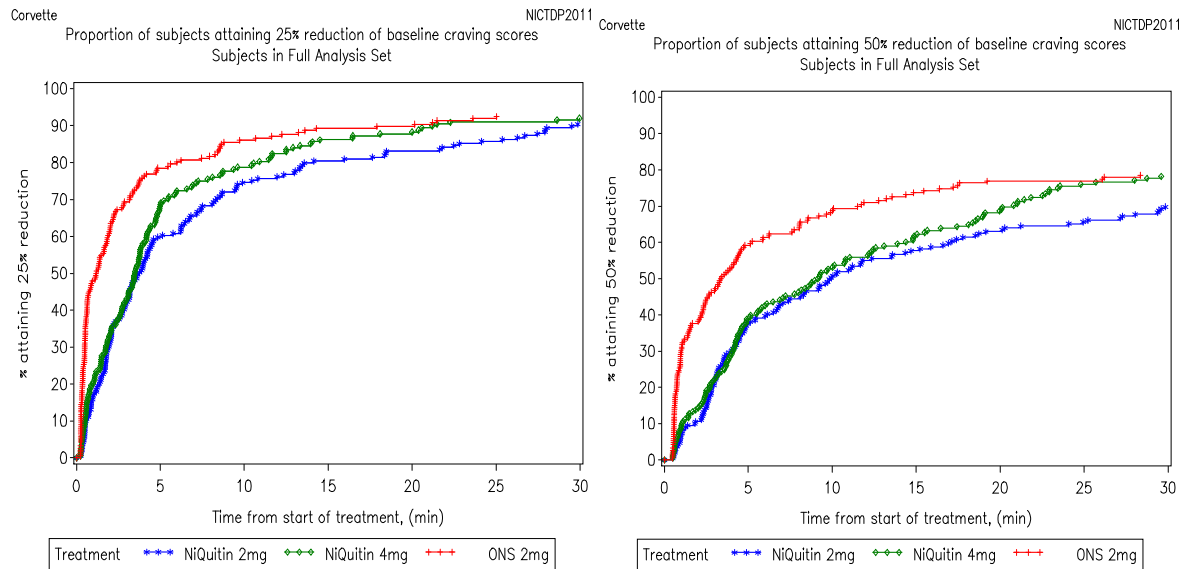
Figure S1: Mean Urges-to-Smoke-vs.-Time Curve after the Afternoon Dose.

**Table S4: Estimated (mean±SD) urges-to-smoke AUCs at 1, 3, 5 and 10 minutes post-administration by treatment, estimated (LSmean±SE) mean average changes in urges-to-smoke scores\* and corresponding comparisons between treatments (estimate [97.5% CI] and Bonferroni-adjusted p-value).**

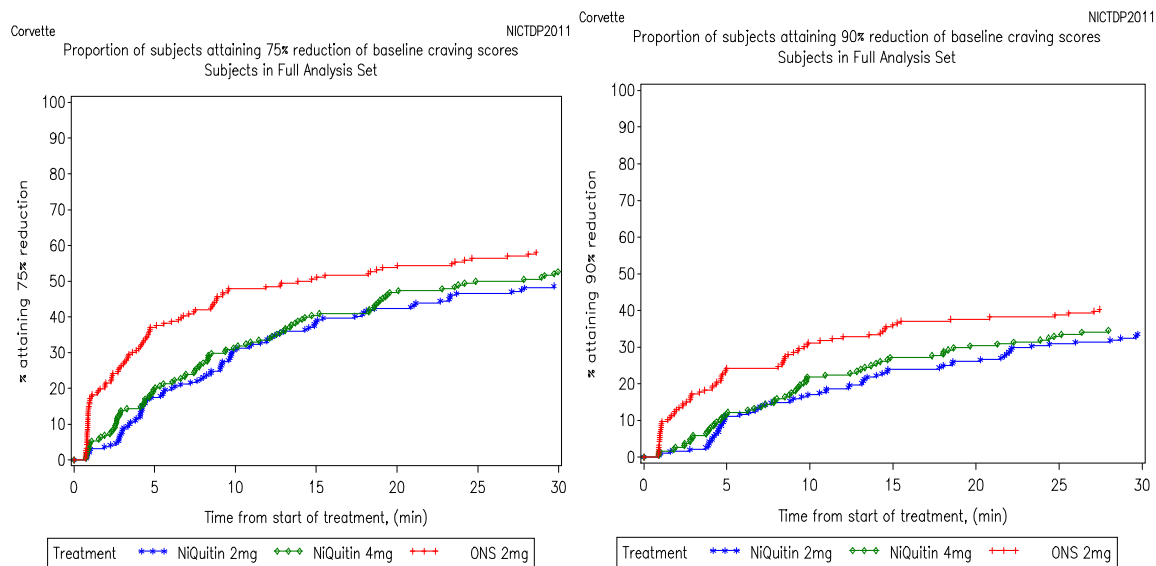
Time	AUC values (mm*min)				Mean Average Score Changes from Baseline (mm)			
	ONS 2 mg	NiQuitin lozenge 2 mg	NiQuitin lozenge 4 mg	ONS 2 mg	NiQuitin lozenge 2 mg	NiQuitin lozenge 4 mg	ONS vs. 2 mg lozenge	ONS vs. 4 mg lozenge
1 min	61.5 ± 23.9	69.0 ± 24.1	67.9 ± 24.4	-11.91 ± 0.72	-3.97 ± 0.72	-4.80 ± 0.72	-7.9 [-9.8, -6.1] p <0.001	-7.1 [-9.0, -5.2] p <0.001
3 min	149 ± 79.6	189 ± 73.5	184 ± 75.4	-23.65 ±1.21	-10.14 ±1.20	-11.62 ±1.20	-13.5 [-16.4, -10.6] p <0.001	-12.0 [-14.9, -9.1] p <0.001
5 min	220 ± 133	289 ± 123	279 ± 124	-29.19 ± 1.32	-15.27 ± 1.31	-17.03 ± 1.31	-13.9 [-16.9, -10.9] p <0.001	-12.2 [-15.2, -9.2] p <0.001
10 min	375 ± 256	497 ± 250	475 ± 243	-35.78 ± 1.45	-23.34 ± 1.44	-25.46 ± 1.44	-12.4 [-15.5, -9.4] p <0.001	-10.3 [-13.4, -7.3] p <0.001

\*The average change in urge-to-smoke score up to *n* minutes is defined as  $AUC_{n\ min} / n$  - baseline urge-to-smoke score (mm).  
The Bonferroni-adjustment amounts to multiplying each nominal p-value with 2 and is also reflected in the coverage of the CIs being 97.5% rather than 95%.





**Figure S2: Proportion of subjects attaining 25% (left graph) and 50% (right graph) of baseline craving scores.**



**Figure S3: Proportion of subjects attaining 75% (left graph) and 90% (right graph) of baseline craving scores during the first 30 minutes after administration.**

Survival curves were statistically significantly different during the two hours of follow-up and favored ONS in each case. Specifically, over the first 30 minutes more subjects perceived a 25%, 50%, 75%, and 90% craving relief with ONS than with NiQuitin<sup>TM</sup> lozenge 2 mg and NiQuitin<sup>TM</sup> lozenge 4 mg (Figures S2 and S3).

A statistical comparison of the proportions of subjects attaining 25%, 50%, 75%, and 90% reduced craving score compared to baseline within 1, 3, 5, and 10 minutes, respectively, further supports the overall survival differences found. For comparisons against both comparators there were statistically significant differences favoring ONS 2 mg for all four degrees of reduction and at all four assessment time points with the exception of the comparison against NiQuitin™ lozenge 4 mg at 10 minutes with respect to 25% reduction, ( $p=0.058$ ).

**Table S5: Estimated Time (minutes) to 25% and 50% Reduction of Baseline Urges to Smoke Scores (median (95% CI)).**

	ONS 2 mg	NiQuitin lozenge 2 mg	NiQuitin lozenge 4 mg
25% reduction	1.19 (0.66-1.73)	3.76 (3.15-4.41)	3.49 (3.00-3.93)
50% reduction	3.40 (2.42-4.53)	9.92 (7.06-14.35)	9.20 (6.09-12.35)

## SAFETY RESULTS:

There were no deaths, other serious adverse events or other significant adverse events in this study. There were no SAEs in this study.

A total of 414 treatment-emergent AEs were reported. Three hundred and forty (340) of these AEs were judged to be possibly treatment-related. Four (4) of the treatment-related AEs were categorized as severe, 85 were moderate and 251 were of mild intensity. The 340 AEs possibly related to treatments can be split into 183, 68, and 89 AEs possibly related to treatments with ONS 1 mg, NiQuitin™ lozenge 2 mg, and NiQuitin™ lozenge 4 mg, respectively.

The body systems most affected by AEs were the respiratory tract, thorax and mediastinum (with hiccups and throat irritation as the most frequently reported AEs) and the gastrointestinal tract (with nausea, dyspepsia and salivary hypersecretion as the most frequently reported AEs). The numbers of subjects experiencing treatment-related AEs are presented in Table S6.

**Table S6: Overview of Number of Subjects Experiencing Treatment-related Adverse Events.**

System organ class	ONS 2 mg	NiQuitin 2 mg	NiQuitin 4 mg
Cardiac disorders	2	1	3
Ear and labyrinth	-	1	-
Eye disorders	1	-	-
Gastrointestinal disorders	64	23	38
General and administration site disorders	5	2	2
Infections and infestations	5	3	2
Musculoskeletal and connective tissue disorders	2	2	2
Nervous system disorders	18	11	6
Psychiatric	-	1	-

System organ class	ONS 2 mg	NiQuitin 2 mg	NiQuitin 4 mg
Respiratory, thoracic and mediastinal	57	18	23
Skin and subcutaneous tissue	5	2	1

**Conclusion(s):**

- ONS 2 mg reduces urges to smoke to a greater extent than NiQuitin<sup>™</sup> lozenge 2 mg and NiQuitin<sup>™</sup> lozenge 4 mg, respectively, during the first 1, 3, and 5 minutes after start of nicotine administration. Thus, ONS acts faster than NiQuitin<sup>™</sup> lozenge.
- Within the first 1, 3 and 5 minutes after start of nicotine administration, more subjects perceive reduced cravings with ONS 2 mg than with NiQuitin<sup>™</sup> lozenge 2 mg or NiQuitin<sup>™</sup> lozenge 4 mg.
- The time to a perceived reduction of cravings is shorter for ONS 2 mg than for NiQuitin<sup>™</sup> lozenge 2 mg and 4 mg.
- There were no observations indicating that the type of AEs caused by ONS might differ importantly from that seen with other nicotine replacement products for use in the mouth. However, in this study, a higher rate of hiccups, dyspepsia, nausea, salivary hypersecretion and throat irritation was seen with single-dose administration of ONS in comparison with NiQuitin<sup>™</sup> lozenge.

There were no protocol deviations with regard to entrance criteria or any other major protocol deviations in this study.

**Report Date: FINAL 05 October 2010; Revised 14 February 2011**