NICOTINE

NICTDP2012

NICOTINE PHARMACODYNAMICS WITH A NEW ORAL NICOTINE REPLACEMENT PRODUCT AND NICOTINE GUM 4 MG. A STUDY IN HEALTHY SMOKERS.

Indication Studied:	For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit.
Developmental Phase of Study:	2
Study Initiation Date (First Subject Enrolled):	26 April 2011
Study Completion Date (Last Subject Completed):	08 July 2011
Status/Date:	FINAL 14 December 2011
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2. SYNOPSIS

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STUDY CENTER(S):

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PUBLICATIONS (REFERENCE): None.

STUDY INITIATION AND COMPLETION DATES: April 26, 2011 – July 08, 2011

PHASE OF DEVELOPMENT: Phase 2

STUDY OBJECTIVE(S): The primary objective of this study was to compare single-dose treatments with NMG 6 mg and Nicorette Freshfruit gum 4 mg with respect to urges to smoke during the first 1 and 3 hours, respectively, after onset of chewing.

Secondary objectives were:

- to conduct between-treatment comparisons of urges to smoke during time intervals beginning at start of chewing and ending 3, 5, and 10 minutes, and 2, 4, and 5 hours, respectively, thereafter,
- to compare the study treatments with respect to subjects' acceptance of the products as a means of NRT,
- to compare the amount of nicotine released from the gums during treatments,
- to evaluate the tolerability of the study treatments.

Methodology

STUDY DESIGN: Treatments comprised single doses of NMG 6 mg and Nicorette Freshfruit gum 4 mg, which were chewed during 30 minutes. All subjects were given both treatments on separate treatment visits in a crossover setting. 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 visit and until the end of each visit. A CO monitor was used as a rough indicator of abstinence from smoking during that time span. Subjects came to the investigation site at approximately 7.45 am on the study days. Breakfast was served at 8.30 am, and study treatments were given at about 9.30 am. The subjects chewed the gums according to instructions from the study personnel. After

chewing, used gums were collected for nicotine analysis. Electronic diaries were used to record the time of start of administration, and to collect urges to smoke and product acceptability data. Urges to smoke were scored on a 100 mm visual analogue scale (VAS) before the start of treatment and during 5 hours thereafter. Subjects were also monitored to capture any adverse events. At the end of each visit, subjects filled in a questionnaire on product acceptability.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED): Two-hundred and fifty (250) subjects were planned and 240 were included in the study. Between 232 and 236 subjects per treatment were analyzed.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy male and female subjects between the ages of 19 and 55 years, inclusive, smoking more than 20 cigarettes daily during at least one year preceding inclusion were enrolled. The subjects had to have a Body Mass Index (BMI) between 17.5 and 32.0 kg/m^2 and a total body weight ≥55 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 S1: Investigational Products and Identity

Investigational Product	Vendor Lot ID / Batch Number	Formula Number	Expiry Date
NMG 6 mg	MF997AX	N/A	June 4, 2012
Nicorette Freshfruit gum 4 mg	MF959A	N/A	June 4, 2012

For treatment with NMG 6 mg and Nicorette Freshfruit 4 mg, subjects were instructed to place the gum in their mouth and chew it slowly with breaks as they considered most convenient for 30 minutes.

DURATION OF TREATMENT: For 228 of the subjects there were no discrepancies between the randomization schedule and the actual dosing schedule. These subjects received two treatments. Twelve subjects withdrew from the study before both treatments had been completed.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: N/A

Criteria for evaluation:

In accordance with the Study Protocol, data from all randomized subjects with at least one valid primary or secondary efficacy recording was included in the Full Analysis Set with respect to pharmacodynamics. All subjects that received any treatment were included in the safety analysis.

EFFICACY EVALUATION: No evaluation of efficacy was made.

PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER EVALUATIONS:

After chewing, used gums were collected for nicotine analysis. Residual amounts of nicotine in the gums after chewing were analyzed using a validated HPLC-method.

Electronic diaries were used to collect urges to smoke and product acceptability data. Urges to smoke were scored on a 100 mm VAS before the start of treatment (at -10 and -3 minutes) and during 5 hours thereafter (at 3, 5, 10, 20, 30, 40, and 50 minutes, and at 1, 2, 3, 4, and 5 hours).

At the end of each visit, subjects filled in a questionnaire on product acceptability.

Subjects were monitored to capture any adverse events that may occur.

SAFETY EVALUATIONS: At screening the following safety evaluations were performed: capillary blood hemoglobin, recording of blood pressure, and pulse rate. In addition, female subjects of childbearing potential were tested for beta-human chorionic gonadotropin before each treatment session.

Authorized study personnel obtained and recorded on the eCRF/CRF all observed or volunteered adverse events, the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study medication. In addition, each study subject was questioned about adverse events. For all adverse events, the investigator pursued and obtained information adequate to determine both the outcome of the adverse event and whether it met the criteria for classification as a serious adverse event. If the adverse event or its sequela persisted, follow-up was required until resolution or stabilization occurred at a level acceptable to the investigator and sponsor.

STATISTICAL METHODS: Pair-wise treatment comparisons with respect to AUC_{1h} and AUC_{3h}, i.e. the area under the urges to smoke-vs.-time curve from time zero (baseline) until 1 hour and until 3 hours, were based on a mixed linear model including sequence, treatment, site and period as fixed effects, and subject, nested within sequence, as random effect. Additionally, the baseline urges to smoke score at time zero were included as a co-varying fixed effect. The baseline urges to smoke score was calculated as the average of the three pre-treatment assessments.

For the pair-wise treatment comparisons with respect to AUC_{3min}, AUC_{5min}, AUC_{10min}, AUC_{2h}, AUC_{4h}, AUC_{5h}, were based on a mixed linear model including sequence, treatment, site and period as fixed effects, and subject, nested within sequence, as random effect. Additionally, the baseline urges to smoke score at time zero was included as a co-varying fixed effect.

Pair-wise treatment comparisons of ordered categorical-scale assessments of acceptability were evaluated with the Wilcoxon signed-rank test applied to derived treatment differences.

The number and percentage of subjects experiencing treatment-related adverse events were summarized by treatment, system organ class, preferred term and severity. Medical Dictionary for Regulatory Activities (MedDRA) was employed as Adverse Event classification system.

RESULTS

SUBJECT DISPOSITION AND DEMOGRAPHY: All included subjects were analyzed for safety. Table S2 gives the subject disposition and the number of subjects analyzed for PD.

Table S2: Subjects Included in the PK/PD Analyses.

Treatment	Completed	Analyzed for PD
NMG 6 mg	232	232
Nicorette Freshfruit gum 4 mg	236	236

Two-hundred and forty (240) subjects, 120 males and 120 females, were included in the study. Two-hundred and thirty-five subjects were white, three were black, one was Asian and one was of other origin. The subjects were smokers consuming an average of 25 cigarettes per day (range 21-38 cigarettes) and had been smokers for 18 years on average (range 2-41 years). Their average age was 35 years (range 19-55 years), and their average BMI was 24 kg/m^2 (range 18-32 kg/m^2). Thus, smoking habits, age and BMI were in accordance with the inclusion criteria.

All subjects were healthy adult volunteers. None of the subjects had conditions or a medical history that the investigator considered sufficient to affect the interpretability of study results 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: Figure S1 displays the average urges-to-smoke-vs.-time curves for the study treatments over the study visit. Table S3 displays the mean average score changes from baselines for the treatments and comparisons between treatments. The amount of nicotine released from gums is presented in Table S4.

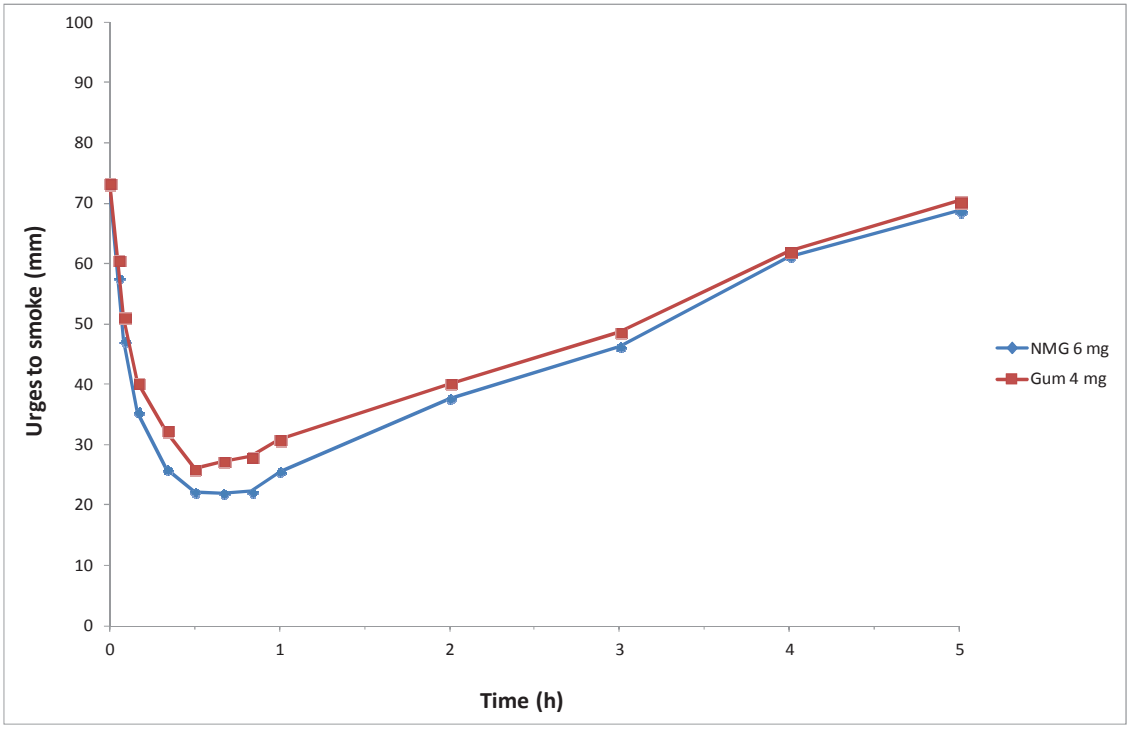

Figure S1: **Mean Urges-to-Smoke-vs.-Time Curve 0-5 hours.**

Table S3: **Estimated mean average changes in urges-to-smoke scores** at 3, 5 and 10 minutes, 1, 2, 3, 4 and 5 hours post-administration by treatment, and corresponding comparisons between treatments (estimate [95% CI] and p-value).**

Time	Mean average score change from baseline (mm)		
	NMG 6 mg	Gum 4 mg	NMG 6 mg vs. Gum 4 mg
3 min	-7.2±9.0	-6.1±8.7	-1.1 [-2.2, -0.1], p 0.034
5 min	-12.2±13.4	-10.4±12.9	-1.9 [-3.4, -0.4], p 0.016
10 min	-21.8±18.6	-18.7±17.5	-3.1 [-5.0, -1.2], p 0.001
60 min	-43.9±23.8	-39.3±23.3	-4.8 [-7.0, -2.6], p<0.001*
120 min	-42.7±23.6	-38.7±23.7	-4.2 [-6.2, -2.1], p<0.001
180 min	-38.8±23.2	-35.5±23.4	-3.4 [-5.8, -1.0], p 0.004*
240 min	-33.9±22.6	-31.1±22.7	-2.9 [-5.0, -0.7], p 0.008

300 min	-28.7±21.8	-26.3±21.5	-2.5 [-4.6, -0.4], p 0.021

* Estimate [97.5% CI] and Bonferroni adjusted p-value.
**Model based least squares mean ± standard error.

Table S4: Amount of Nicotine Released from Gums (mg).

	NMG 6 mg	**Gum 4 mg**
Mean ± SD	4.00 ± 1.28	2.64 ± 0.90
(Min - Max)	(0.3-6.2)	(-0.1-4.2)

SAFETY RESULTS: There were no SAEs in this study.

A total of 173 treatment-emergent AEs were reported. One-hundred and fifty-two of these AEs were judged to be possibly, probably or very likely related to treatment. None of the treatment-related AEs were categorized as severe, 17 were moderate and 135 were of mild intensity.

The numbers of subjects reporting AEs judged to be possibly, probably or very likely related to treatment are presented in Table S5.

Ninety-five (95) subjects recorded treatment related AEs with NMG 6 mg, and 57 with Nicorette Freshfruit gum 4 mg.

The body systems most affected by AEs for the study treatments were the gastrointestinal tract with nausea and dyspepsia being the most frequently reported AEs, and the respiratory tract, thorax and mediastinum with throat irritation and hiccups being the most frequently reported AEs.

Table S5: Overview of Number of Subjects Reporting Adverse Events Possibly, Probably or Very Likely Related to Treatment.

System organ class	**NMG 6 mg**	**Gum 4 mg**
Subjects with at least 1 AE	63	44
Cardiac disorders	3	2
Gastrointestinal disorders	38	24
General disorders and administration site conditions	1	1
Infections and infestations	-	1
Musculoskeletal and connective tissues disorders	1	-
Nervous system disorders	7	6
Respiratory, thoracic and mediastinal disorders	31	17
Skin and subcutaneous tissue disorders	2	3

CONCLUSION(S):

- NMG 6 mg reduces urges to smoke more than Nicorette Freshfruit gum 4 mg during the first 1 and 3 hours after start of administration. Thus, NMG 6 mg provides a stronger craving relief than Nicorette Freshfruit gum 4 mg.
- NMG 6 mg reduces urges to smoke more than Nicorette Freshfruit gum 4 mg during the first 3, 5 and 10 minutes, respectively, after start of administration. Thus, treatment with NMG 6 mg provides a faster craving relief than Nicorette Freshfruit gum 4 mg.
- NMG 6 mg reduces urges to smoke more than Nicorette Freshfruit gum 4 mg during 2, 4 and 5 hours, respectively, after start of administration.
- There were no indications that the types of AE of the investigational products differ from those of other oral nicotine replacement products. As expected, some types of AEs occurred more frequently with NMG 6 mg than with Nicorette Freshfruit gum 4 mg.

REPORT DATE: FINAL 14 December 2011