## 2. SYNOPSIS

**INVESTIGATOR**: [redacted]

**STUDY CENTER:** [redacted]

**PUBLICATIONS (REFERENCE):** None

**STUDY INITIATION AND COMPLETION DATES:** 20 March 2017 to 29 June 2017

**PHASE OF DEVELOPMENT:** Phase 1

**STUDY OBJECTIVES**

The primary objectives of this study were:

- to demonstrate bioequivalence between Nicorette® Strongmint lozenge 4 mg (NSL 4 mg) and NiQuitin® Minimint lozenge 4 mg (NML 4 mg), with respect to single-dose pharmacokinetics of nicotine,
- to further describe the nicotine single-dose pharmacokinetics of the investigational products, and
- to assess the time until complete dissolution of each treatment´s lozenge in the mouth.

The secondary objective was:

- to evaluate the tolerability of the treatments in terms of spontaneously reported and observed AEs.

**METHODOLOGY**

**STUDY DESIGN**

This was a single-dose, two-period crossover, randomized, fasting, open-label, bioequivalence study planned for 244 healthy male and female volunteers, aged between 18 and 45 years, inclusive.

Single doses of NSL 4 mg (i.e. test product) and NML 4 mg (i.e. reference product) were administered in a standardized mode, on two separate treatment visits. A washout period of at least 48 hours separated the treatment administrations.

An abstinence period of 12 hours including an overnight stay at the clinic was required at both treatment occasions.

Blood for pharmacokinetic analyses was drawn pre-dose (i.e. within 5 minutes before drug administration) and at 10, 15, 20, 30, 40, 50, and 60 minutes, as well as 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after start of drug administration. Thus, 17 samples were collected per treatment visit. Self-reported lozenge dissolution times were registered.

Subjects were monitored throughout the study period to capture any AEs that occurred.

**NUMBER OF SUBJECTS (PLANNED AND ANALYZED)**

Two-hundred and forty-four (244) subjects, 140 males and 104 females, were randomized to treatment. In this study, 223 subjects had at least some valid PK data and were therefore included in the full analysis set. Two-hundred and one (201) subjects had evaluable $cC_{max}$ and $cAUC_t$ values for both treatments and were therefore included in the bioequivalence assessment.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION**

Healthy male and female subjects between the ages of 18 and 45 years, inclusive, were enrolled. The subjects had to have a Body Mass Index (BMI) between 18.5 and 30 $kg/m^2$. Subjects were to be smokers of at least 10 tobacco cigarettes per day and were to have done so for at least 3 months preceding inclusion, and being motivated to quit smoking. Females had to be in a postmenopausal state or in a premenopausal/perimenopausal state with an effective means of contraception. Males had to have no pregnant or lactating spouse or partner at screening and willingness to utilize effective methods of birth control for at least 3 months before the study, during the study and for 30 days after the last dose of study drug.

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

Table S1 provides information about the investigational products.

**Table S1: Identity of Investigational Products**

| | **Treatment A (NSL 4 mg)** | **Treatment B (NML 4 mg)** |
|---|---|---|
| **Compound Name** | Nicotine | Nicotine |
| **Product Name** | Nicorette® Strongmint | NiQuitin® Minimint |
| **Dosage Form** | Lozenge | Lozenge |
| **Unit Dose** | 4 mg | 4 mg |
| **Route of Administration** | Oromucosal | Oromucosal |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

Subjects were instructed to place the lozenge in their mouth, to occasionally move it from side to side until complete dissolution, and not to chew or swallow the lozenges.

## DURATION OF TREATMENT

Each of the two treatments were given on separate days, which were separated by washout periods without NRT, lasting for at least 48 hours.

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

## CRITERIA FOR EVALUATION

### Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations

All randomized subjects with any valid pharmacokinetic parameter data from at least one of the two investigational products and without protocol deviations having an impact on the nicotine pharmacokinetics, were included in the statistical evaluation.

### Safety Evaluations

All subjects that received any treatment were included in the safety analysis.

## STATISTICAL METHODS

For all pharmacokinetic parameters, descriptive summary measures were presented by treatment. The pharmacokinetic parameters were summarized based on both the measured values as well as baseline corrected nicotine values. For continuous variables, statistical summaries were presented. In addition, geometric mean values and coefficients of variation were calculated for the maximum observed nicotine plasma concentration corrected for baseline nicotine concentrations ($cC_{max}$), the baseline corrected areas under nicotine plasma concentration vs. time curves from start of administration until the last measurable concentration ($cAUC_t$) and until infinity ($cAUC_{inf}$). For $t_{max}$, the frequency distribution was additionally tabulated by treatment.

In the statistical model-fitting process, for each of the three analyzed pharmacokinetic parameters ($cC_{max}$, $cAUC_t$ and $cAUC_{inf}$), only data from subjects with valid parameter values for both compared treatments were included. Statistical comparisons of NSL 4 mg and NML 4 mg with respect to these pharmacokinetic endpoints, were in each case based on a linear model for log transformed (natural log) pharmacokinetic parameter data. The log transformed data were assumed to follow a normal distribution. For each parameter evaluation, the statistical model included covariate adjustments for period and treatment sequence, and subject, nested within sequence, as fixed effects. In addition, the logarithm of the baseline nicotine concentration, log ($C_0$), was included as a covariate in the model. Carry-over effects were assumed ignorable. In each case an interval estimate with confidence level 90% for the treatment geometric mean ratio was calculated from the fitted model.

Bioequivalence between NSL 4 mg and NML 4 mg was concluded, based on linear statistical models for the natural logarithms of the primary pharmacokinetic parameters, if:

- the model-based 90% confidence interval for the treatment geometric mean ratio for $cC_{max}$ was contained in the equivalence interval (0.80, 1.25), and
- the model-based 90% confidence interval for the treatment geometric mean ratio for $cAUC_t$, was contained in the equivalence interval (0.80, 1.25).

All AEs reported during the AE reporting period was to be listed by subject ID and last treatment administered before the AE. Any SAE was listed separately. The number and percentage of subjects experiencing AEs were tabulated by treatment, system organ class, and preferred term. In addition, number and percentage of subjects' experienced AEs with a possible, probable, or very likely relation the investigational product were separately tabulated by treatment, system organ class, preferred term, and worst recorded severity. Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used as AE classification system.

## RESULTS

### SUBJECT DISPOSITION AND DEMOGRAPHY

The number of subjects included in the assessment are displayed in Table S2.

**Table S2: Evaluable Subjects**

| Treatment | $cC_{max}$ | $cAUC_t$ |
|---|---|---|
| NSL 4 mg | 207 | 208 |
| NML 4 mg | 213 | 213 |

Two-hundred and forty-four (244) subjects, 140 males and 104 females, were included in the study (Table 14.1.2). All were white. Their average age was 27.5 years (range 18-45 years) and their average BMI was 23.3 $kg/m^2$ (range 18.5-29.9 $kg/m^2$). The subjects were smokers consuming on average 16.4 cigarettes per day (range 10-40 cigarettes) and they had been smokers for 8.4 years on average (range 1-30 years). Thus, age, BMI and smoking habits 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 PI considered would affect the conduct of the study or to represent a potential risk to the subject during study participation.

Seven (7) subjects did not receive any treatment (due to discontinuation prior to the first treatment) and were therefore not included in the safety evaluation. Thus, 237 were analyzed with respect to safety information.

## PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER RESULTS

### Pharmacokinetic

Figure S1 displays the average plasma concentration profiles of nicotine for the study treatments, plotted over 12 hours after start of administration.

Observed geometric means of $cC_{max}$, $cAUC_t$ and $cAUC_{inf}$ are displayed in Table S3. Model-based estimates and corresponding 90% confidence intervals for the ratios of the population geometric means of the pharmacokinetic parameters between the NSL 4 mg and NML 4 mg are presented in Table S4.

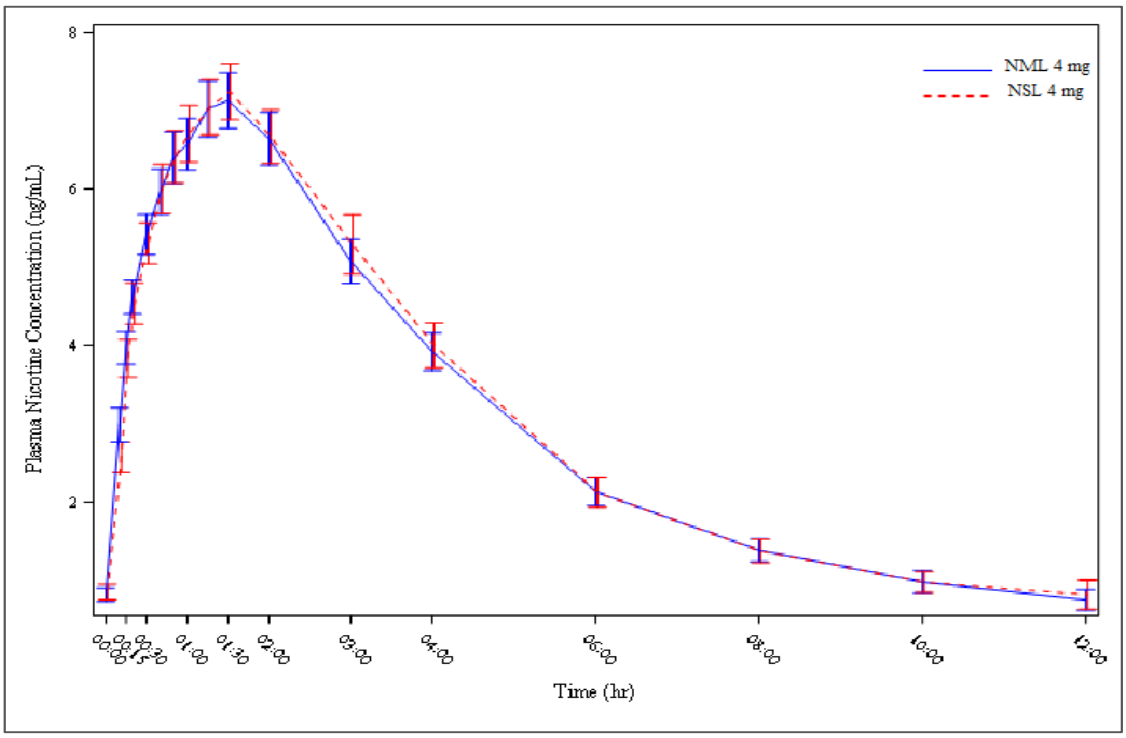

**Figure S1: Mean Nicotine Plasma Concentration vs. Time Profiles over 12 hours after Start of Administration (Mean Values with 95% CI)**

**Table S3: Pharmacokinetic Parameters Observed Geometric Means (CV%)**

| PK parameter | NML 4 mg (n=213) | NSL 4 mg (n=207-208) |
|---|---|---|
| **$cC_{max}$ (ng/mL)** | 7.01 (36.57) | 7.10 (35.85) |
| **$cAUC_t$ (ng/mLxhr)** | 28.28 (42.70) | 27.70 (44.28) |
| **$cAUC_{inf}$ (ng/mLxhr)** | 30.95 (43.11) | 30.53 (44.66) |

**Table S4: Pharmacokinetic Parameters Estimated Ratios of Geometric Means**

| PK Parameter | NSL 4 mg vs. NML 4 mg (n=201) | |
|---|---|---|
| | **Ratio (%)** | **90% CI (%)** |
| **$cC_{max}$** | 101.0 | 98.2 – 103.9 |
| **$cAUC_t$** | 100.4 | 97.6 – 103.4 |
| **$cAUC_{inf}$** | 101.1 | 98.3 – 104.0 |

Table S5 provides across-subject averages and standard deviations for times until complete dissolution of the tablets in the mouth.

**Table S5: Dissolution Time (Minutes)**

| | Mean | SD | Median | Min - Max |
|---|---|---|---|---|
| **NML 4 mg** (n=222) | 9.0 | 4.39 | 8.0 | 4 – 41 |
| **NSL 4 mg** (n=218) | 11.0 | 4.50 | 10.0 | 4 – 34 |

**SAFETY RESULTS**

In total, 294 treatment-emergent AEs were reported. Two-hundred thirty-six (236) of these were considered to be "possibly", "probably" or "very likely" related to treatment Table S6. All of these were considered "mild" in severity. Two subjects withdrew from the study due to AE.

No SAE was reported during the study. There were no deaths or other significant AEs.

Eighty-six (86) subjects experienced at least one AE possibly, probably or very likely related to treatment with NML 4 mg. The corresponding numbers with NSL 4 mg was 91.

Gastrointestinal Disorders represented the most commonly reported AEs, followed by Respiratory, Thoracic and Mediastinal Disorders. In general, AEs were consistent with current understanding of the safety profile for nicotine lozenges.

**Table S6: Number of Subjects with AEs Possibly, Probably or Very Likely Related to Treatment**

| System Organ Class | Adverse Event (Preferred Term) | NML 4 mg (n=230) | NSL 4 mg (n=234) |
|---|---|---|---|
| Gastrointestinal disorders | Nausea | 25 | 35 |
| | Salivary hypersecretion | 3 | 4 |
| | Eructation | - | 2 |
| | Dry mouth | - | 1 |
| Respiratory, thoracic and mediastinal disorders | Throat irritation | 16 | 27 |
| | Hiccups | 14 | 8 |
| Nervous system disorders | Dizziness | 20 | 15 |
| | Headache | 2 | 4 |
| | Parosmia | - | 1 |
| | Syncope | 1 | - |
| General disorders and administration site conditions | Sensation of foreign body | 19 | 21 |
| | Chest pain | 0 | 2 |
| Cardiac disorders | Tachycardia | 4 | 7 |
| Vascular disorder | Pallor | 1 | 1 |
| | Hot flush | - | 1 |
| Investigations | Blood pressure decreased | 1 | - |
| | Eosinophil count increased | 1 | - |

## CONCLUSIONS

- Bioequivalence was demonstrated between Nicorette® Strongmint lozenge 4 mg and NiQuitin® Minimint lozenge 4 mg.

- On average, the NiQuitin® Minimint lozenge 4 mg dissolved in 9 minutes. Nicorette® Strongmint lozenge 4 mg dissolved in 11 minutes.
- The reporting frequency of AEs within this study remains consistent with previous similar studies.

**REPORT DATE:** 14 June 2018