Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate dihydrate lozenges (Nicotinell®)

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Abstract

Background
The use of nicotine replacement therapy (NRT) can almost double the chances of success for smokers to quit. Choosing the form most preferred by the smoker can further improve the chances of success. A novel oral formulation, (lozenge containing nicotine bitartrate dihydrate) has been developed to address this requirement.

Methods
Three pharmacokinetic (PK), one safety and two efficacy studies were carried out with Nicotinell lozenges. PK trials were: (1) a single-dose, three-way crossover study comparing 1 and 2 mg lozenges with 2 mg nicotine gum; (2) a multiple-dose, two-way crossover study comparing 1 mg lozenge with 2 mg gum; (3) a multiple-dose, three-way crossover study comparing 1 and 2 mg lozenges with 4 mg gum. Safety trial: (4) a single dose study to assess the safety of swallowing up to 12 lozenges containing 1 mg nicotine. Efficacy trials: two efficacy studies in (5) France and (6) the USA, including more than 900 smokers followed-up for up to one year, conducted with the 1 mg lozenge.

Results
The results of the individual PK trials showed that the 1 mg Nicotinell lozenge is bioequivalent to 2 mg polacrilex gums, as demonstrated by similar blood PK parameters (t_{max}, C_{max}, AUC). The 2 mg lozenge was found to deliver quantities of nicotine that were intermediate between those delivered by 2 and 4 mg polacrilex gums. Nicotinell lozenges were found to be safe with mainly mild and reversible adverse events. The safety of the 1 mg lozenge formulation, even when misused, and
its efficacy for smoking cessation in comparison with placebo were also demonstrated.

Conclusions

Nicotinell 1mg lozenge is bioequivalent to 2 mg polacrilex gum, whereas the 2 mg lozenge provides nicotine levels between those of 2 and 4 mg polacrilex gums. Up to 12 nicotine 1 mg lozenges can be swallowed at once without any serious adverse event. Given their proven clinical efficacy and advantageous safety profile, these Nicotinell lozenges present an attractive alternative for the smoker aiming to quit.
Background

Smoking is still the largest preventable cause of death and disease in the developed world and increases the risk for cancer, cardiovascular and lung diseases, among others [1-3]. Accordingly, smoking cessation provides immediate and lasting benefits to public health [4-6]. However, relatively few smokers succeed in quitting each year [7]. Nicotine replacement therapy (NRT) helps smokers quit by providing nicotine at levels usually lower than those obtained through smoking and without the toxins contained in tobacco smoke. NRT can reduce the craving for nicotine and the nicotine withdrawal symptoms which might otherwise jeopardize the smoking cessation efforts [8]. NRT has a well established success record [9] and its use is endorsed by health authorities [4, 10-12].

Several forms of NRT are available for smokers to choose from, according to their specific needs and preferences [8, 13]. Beside nicotine patches, which deliver nicotine slowly and continuously through the skin, a number of acute dosing formulations have been developed, which allow smokers to self-administer the amount of nicotine needed, in order to achieve a consistent concentration of nicotine in the blood, and to ward off acute urges to smoke (‘rescue medication’ use) [14]. The first available acute dosing form was nicotine-containing polacrilex chewing-gum, which was launched in the 1980s. More recent additions are the vapor inhaler, sublingual tablet, lozenge (all for oral nicotine administration), and nasal spray (uptake via the nasal mucosa) [15]. The efficacy and safety of nicotine lozenges containing 2 or 4 mg of nicotine coupled to a polacrilex resin, from which it is released upon dissolution of the lozenge in the mouth, have been described and compared with nicotine-containing gums also using a polacrilex resin [16]. The efficacy of the Nicotinell lozenges studied in this review has
previously been described [17-18]. The versatility of lozenges has also been demonstrated in the treatment of smokers who had previously failed to quit on other NRT products, and of both very heavy and moderate/light smokers [19-21]. Indeed, when compared to the gums, lozenges are characterized by a number of advantages, such as fewer potential oral health limitations (e.g. dental works or temporomandibular joint pain), better social acceptance (e.g. at workplaces), and greater ease of use as they do not require chewing. As opposed to patches, lozenges provide all the advantages of acute dosing forms described above [22], including the possibility of self-adaptation of the dose and some degree of behavioral activity and sensory stimulation, which might be crucial for smokers trying to quit.

Despite considerable literature, there are few published studies comparing directly different NRT products [9]. In addition, pharmacokinetic (PK) data on nicotine lozenges in the literature remain scarce [23]. The present review provides the first comprehensive description of the PK profiles of 1 and 2 mg Nicotinell lozenges in comparison with 2 and 4 mg nicotine gums. In addition, the efficacy and safety of the 1 mg Nicotinell lozenge in smoking cessation are documented.
Methods

General

All presented studies were carried out in compliance with the Declaration of Helsinki and its amendments and Good Clinical Practices. All protocols were accepted by local ethics committees (Table 1). All subjects provided written informed consent before enrolment in the studies.

Participants to the studies were adult, healthy smokers usually smoking at least 20 cigarettes per day in the PK trials, or at least 10 cigarettes per day in the safety trial. During the PK and safety trials, participants were maintained under highly controlled conditions, including standardized food and fluid intake, restricted physical activity, and cigarette abstinence. Non-smoking compliance was controlled by measurement of carbon monoxide (CO) in expired air. Blood samples were collected at planned time-points. Concentrations of nicotine and cotinine in plasma or urine were determined by validated GC-MS methods with limits of quantification at respectively 1 ng/ml and 10 ng/ml for nicotine and cotinine (LC-MS/MS for the multiple-dose study comparing 1 and 2 mg lozenges with 4 mg gum). Residual nicotine contents in the chewed gums (or sucked lozenges) after use were determined by HPLC.

Single-dose pilot study comparing 1 and 2 mg lozenges with 2 mg gum

This was a single-center, open-label, single-dose, randomized, three-way, crossover pilot study in nine male volunteers to assess the PK parameters of 1mg Nicotinell lozenges (containing 3.07 mg nicotine bitartrate dihydrate equivalent to 1 mg nicotine base), 2mg Nicotinell lozenges (containing 6.134 mg nicotine bitartrate dihydrate equivalent to 2 mg nicotine base), and 2 mg nicotine gums (Nicorette® gums; Pharmacia A.B.; containing 10 mg nicotine carboxylate cation resin equivalent to
2 mg nicotine base). The same brand of comparator gum was used throughout the ensuing clinical development. Subjects were randomized to one of the three groups and received one piece of trial medication during each of the three 32-hour observation periods, which always started with a 24-hour non-smoking phase, and were separated by 7-day washouts. Lozenges were sucked and gums chewed for 30 min according to a controlled schedule, and remainders were collected to measure drug delivery. In this pilot study, lozenges were not completely dissolved at the end of 30 min, therefore the sucking pattern was modified for subsequent studies. Blood was drawn before dosing and at 15, 30, 45 min, 1, 1.25, 1.5, 2, 3, 4, 6, and 8 h after dosing. Urine was collected during the 24 h run-in preceding administration and between 0-4 h and 4-8 h after dosing. Main criteria for comparison between different drugs were \( \text{AUC}_{0-c} \) and \( C_{\text{max}} \), which were corrected for 100% drug delivery from lozenge. Ln-transformed values were submitted to 4-factor ANOVA (sequence, subject, period, treatment).

Multiple-dose study comparing 1 mg lozenge with 2 mg gum

This was a single-center, open-label, multiple-dose, randomized, two-way, crossover PK study in 24 male volunteers that compared 1 mg Nicotinell lozenges with 2 mg nicotine polacrilex gums. Two 2-day observation periods were separated by a 7-day washout and each period started with a 22-hour run-in phase without smoking, followed by a 12-hour dosing phase and a 23-hour sampling phase. Twelve doses of nicotine were administered, i.e. one per hour from \( t=0 \) to \( t=11 \). Lozenges were sucked until complete dissolution, and the time needed to achieve this (usually about 30 min) was reported. Gums were chewed for 30 min according to a schedule monitored by a computer-controlled beeper, and residues were collected and frozen for HPLC analysis. Blood was drawn pre-dose, 15, 30 and 45 min after the first dose. In
addition, blood was drawn before each new dose (at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11h) and after the last dose at 11.25, 11.5, 11.75, 12, 12.25, 12.5, 13, 13.5, 14, 15, 17, 19, 21, and 23h (all times after first dose).

Main criteria for comparison of nicotine PK at steady state were $C_{\text{max}}$, $t_{\text{max}}$ and $\text{AUC}_{11-12}$ (AUC during one dosing interval). Secondary criteria were first dose data ($C_{\text{max}}$, $t_{\text{max}}$, $\text{AUC}_{0-1}$), $C_{\text{min}}$ before each dose and $t_{1/2}$ after the last dose. In addition, urinary and saliva pH variations were assessed and safety was controlled through assessment of cardiovascular parameters (blood pressure (BP), heart rate (HR), and ECG), standard laboratory tests and incidence of adverse events (AEs). $C_{\text{max}}$ and $\text{AUC}_{11-12}$, ln-transformed values were submitted to 4-factor ANOVA (sequence, subject, period, treatment). A 90% confidence interval (CI) was constructed for $C_{\text{max}}$ and $\text{AUC}_{11-12}$ and the primary criterion for relative bioequivalence was that the 90% confidence limits fall within the interval (0.80-1.25) of the standard 20% bioequivalence acceptance range (BAR). If needed, the enlarged 30% BAR (0.7-1.43) was also applied.

Multiple-dose study comparing 1 and 2 mg lozenges with 4 mg gum

This was a single-center, open-label, multiple-dose, randomized, three-way, crossover PK study in 31 male volunteers. Its primary objectives were: (1) to confirm the dose-concentration proportionality between Nicotinell 1 and 2 mg lozenges and (2) to compare nicotine systemic exposure by Nicotinell 2 mg lozenge with that of Nicorette 4 mg gum. Secondary objectives were the completion of the PK profile of the 2 mg Nicotinell lozenge and the comparison of clinical safety of the three nicotine formulations. There were three treatment periods of 12 h (one for each product), separated by 7-day washout periods. Smoking was prohibited during the 24 h preceding treatment and until leaving the study center. During each treatment period,
a total of twelve doses of nicotine were administered at a rate of 1 dose per hour. Lozenges were sucked until complete dissolution and gums were chewed for 30 min at 60 chews/min (timed using a calibrated metronome) while the subjects remained in a seated position. Blood samples for determination of plasma nicotine and cotinine concentrations were drawn pre-dose and at 7 and 9 h. After intake of the last dose (11 h), blood was drawn at 11.25, 11.5, 11.75, 12.5, 13, 14, 15, 17, 19, 21, and 23 h. Tolerability was assessed by reporting of AEs. Primary PK parameters for evaluation were steady state data after the last dose (AUC_{11-12}, C_{max} and t_{max}). For the comparison between 1 and 2 mg lozenges (dose proportionality) and between 2 mg lozenge and 4 mg gum, ln-transformed values for C_{max} and AUC_{11-12} were submitted to 4-factor ANOVA (sequence, subject, period, treatment). Relative bioequivalence was determined by construction of 90% CIs and application of the standard 20% (0.80-1.25) and enlarged 30% (0.7-1.43) BARs for C_{max} and AUC_{11-12}, and by Friedman ANOVA for t_{max}. In addition, complete safety and tolerability data were collected, including physical examination and vital signs, cardiovascular parameters, standard laboratory tests and incidence of AEs.

Safety of 1 mg lozenge after swallowing

This was a single-center, open-label, escalating-dose, sequential group safety study with 24 volunteers of both sexes. The participants were divided into three groups of eight: subjects in group A swallowed three lozenges, in group B six lozenges, and in group C 12 lozenges. For every group, subjects were included in two steps: first, two volunteers were assessed, and if the administered dose was well tolerated the other six volunteers were included. Each dose level was followed by a 2-day observation period, including a 12 h period after dosing during which smoking was prohibited. Lozenges were swallowed as a single dose with 250 ml of water. Safety was assessed
by examination of the plasma nicotine levels, subjects’ clinical status, standard laboratory testing, gastric motility test (only the first two subjects of each group) and AEs reporting. Blood for determination of plasma nicotine levels was drawn pre-dose and 10, 20, 30, 40, 50 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 13, 16 and 48 h post-dose.

Criteria for safety evaluation were as follows: (1) \( C_{\text{max}} \) and \( t_{\text{max}} \) after each dose, as well as \( \text{AUC}_{10\text{min}-12\text{h}} \) for nicotine PK; (2) BP, HR, ECG, and physical examination for clinical status; (3) hematology, biochemistry (including hepatic parameters, serology and urinalysis), carboxyhemoglobin, carcinoembryonic antigen, and urinary cotinine and catecholamine levels for laboratory testing; and (4) gastric emptying and antral motor activity for gastric motility. Nicotine PK parameters were analyzed by summary statistics of all nicotine concentrations, \( \text{AUC} \), \( t_{\text{max}} \), \( C_{\text{max}} \), and comparison of PK values by one-way ANOVA. BP and HR were analyzed by an ANOVA GLM model for systolic and diastolic values, as well as for the difference (systolic – diastolic); factors for ANOVA were subject, period and treatment. All other parameters were analyzed within each treatment group by Wilcoxon paired test (pre-vs. post-dosing). Post-entry differences of each treatment group were compared by one-way ANOVA or Kruskal-Wallis test, as appropriate. For all parameters, McNemar test was used to detect volunteers who changed their status from entry to post-dosing in terms of normal range limits.

**Efficacy trials with 1 mg lozenge**

Two large phase 3 studies were performed to assess the efficacy of 1 mg Nicotinell lozenge in smoking cessation, one in France (37 trial centers; AFSSAPS trial registration number: 980324) and one in the USA (3 trial centers; registration number 905.1295). The 2 trials had a double-blind, placebo-controlled, randomized, parallel
groups design. The patients, respectively for the French and the American trials, were
distributed as follows: (1) randomized and received at least one treatment: 436 and
460 patients, (2) received verum lozenge: 214 and 230 patients, (3) received placebo
lozenges: 222 and 230 subjects. Eligible subjects were healthy smokers of both sexes
and aged ≥18 years, motivated to quit. To have a global view on the lozenge efficacy
over a wide range of dependence levels, patients had either a medium to high
dependence of smoking in the French study (Fagerström Test for Nicotine
Dependence (FTND) score of 4-7 and smoking 10-30 cigarettes / day), or a high to
very high dependence in the US study (FTND score ≥6 and smoking 20-40 cigarettes
/ day). Subjects were advised to suck between 8 and 25 lozenges each day (dosage
self-adjusted by subjects) for six weeks, followed by complete weaning over the next
six weeks with a suggested decrease of one lozenge per day relative to the dose at
week 6. Subjects attended the study site at screening (baseline), biweekly or weekly
up to week 6, and then at week 12, and 26. After week 6, only abstinent subjects were
continuously followed-up. At visits, smoking status (exhaled-breath CO), BP, HR,
weight, and AEs were recorded. From weeks 0-6 (France) or 0-12 (USA), subjects
recorded daily in a diary the number of lozenges used and of cigarettes smoked (if
any), plus any withdrawal symptoms experienced. During the study no formal
behavioral counselling was offered to patients. The primary efficacy outcome
measure was the proportion of patients continuously and completely abstinent (no
cigarettes and CO <10 ppm) during the four weeks preceding week 6. Secondary
efficacy outcomes were the point prevalence abstinence rates at the visits on week 12
and on week 24, the evolution of withdrawal symptom scores, and partial abstinence
rates (partial abstinence defined as smoking of ≤1 cigarette per day and ≤7 cigarettes
per week, and CO <10 ppm) on week 6, 12 and 24. Safety of treatment (AEs, BP, HR,
weight) and levels of urine nicotine metabolites (French study only) were further outcome measures. Efficacy was analyzed using Cochran-Mantel-Haenszel statistic, stratified by study center. Comparison between treatments was made using the Cochran-Mantel-Haenszel chi-square test, after adjusting for pooled centers. The experimental details and results of the French trial have previously been described [17, 18].
Results

Single dose pilot study: PK comparison of 1 and 2 mg lozenges with 2 mg gum

Key PK results are summarized in Table 2. The sucking pattern in this trial did not result in full dissolution of the lozenges and only approximately 67% of their nicotine content was released. Thus, a correction was applied to calculate $C_{\text{max}}$ and $AUC_{0-\infty}$ for a fully dissolved lozenge. This was deemed appropriate because lozenges are designed to be fully sucked out by users. The adjusted values for $C_{\text{max}}$ and $AUC_{0-\infty}$ of 1 mg lozenge and 2 mg gum were similar and thus indicated comparable nicotine delivery from these two formulations. In addition, comparison of PK parameters of 1 and 2 mg lozenges demonstrated dose-concentration proportionality between these doses, which was verified in an ensuing multiple-dose study (see below).

During metabolization, nicotine is converted into several metabolites including cotinine, which are finally excreted in urine. Further support for comparable PK properties of 1 mg lozenge and 2 mg gum came from mean plasma cotinine kinetics, including $C_{\text{max}}$ (19.9 → adjusted 29.7 ng/ml with lozenge vs. 30.2 ng/ml with gum), $AUC_{0-\text{t}}$ (102 → 152 h.ng/ml vs. 153 h.ng/ml), $t_{\text{max}}$ (5.2 vs. 5.3 h), and $t_{1/2}$ (9.4 vs. 11.4 h). Similarly, urinary cotinine values were comparable between 1 mg lozenge and 2 mg gum, and dose-concentration relationship was apparent for urinary cotinine excretion after dosing with 1 mg vs. 2 mg lozenges (data not shown). Among the 18 AEs observed, only 2 were considered to be related to study drug (throat irritation with 2 mg lozenge and gum), but none was serious. No other clinically relevant abnormalities were noted with any of the products.
Bioequivalence of 1 mg lozenge and 2 mg gum at steady state

As the pilot study suggested bioequivalence of 1 mg lozenges and 2 mg gums, this trial was designed to confirm this bioequivalence between these two formulations, focusing on PK characteristics after multiple doses and at steady state. Median duration for complete dissolution of lozenges over the entire study period was 29.25 min (range 27-31 min). The mean amount of nicotine extracted from the gums increased from 1.0 mg at dose 1 to 1.13 mg at dose 12 (+13%). Therefore, an adjustment was applied to the amount of nicotine actually delivered by gums at different time-points in order to ensure consistent statistical analysis of PK parameters. Both NRT products led to an increase in saliva pH after dosing, the lozenge having a significantly higher buffering power than the gum (data not shown), which is known to favor a non-ionized state of nicotine and its absorption [25-26]. As expected, median $t_{\text{max}}$ (0.76 vs. 0.75 h), mean $C_{\text{max}}$ (4.2 ± 1.8 vs. 5.0 ± 1.6 ng/ml) and $\text{AUC}_{0-1}$ (2.9 ± 1.4 vs. 3.5 ± 1.3 h.ng/ml) were similar for lozenge and gum after the first dose (0-1 h).

Plotting of plasma nicotine concentrations over time after repeated administration of Nicotinell 1 mg lozenges and 2 mg polacrilex gums revealed that the plateau of concentration was reached after intake of six doses (Figure 1). The blood draws after the last dose allowed to determine PK characteristics at steady state. The observed kinetics suggested that intake of lozenges or gums under these conditions lead to “peak-trough” kinetics of nicotine similar to those observed during day-time in dependent smokers having cigarettes, but much reduced in intensity. Indeed, the highest concentration (approximately 11 ng/ml) obtained with the tested formulations corresponds to the lower end of the range of blood nicotine levels (10-50 ng/ml) observed in smokers in the afternoon (i.e. at steady state) [14].
The determined values for $C_{\text{max}}$, $t_{\text{max}}$ and AUC$_{11-12}$ showed that nicotine delivery characteristics of 1 mg Nicotinell lozenge and 2 mg polacrilex gum at steady state were comparable (Table 3). When bioequivalence was statistically assessed, the 90% CIs for $C_{\text{max}}$ and AUC$_{11-12}$ remained within the standard 20% BAR (0.80-1.25), indicating bioequivalence of the 1 mg lozenge and the 2 mg gum under the studied conditions. When unadjusted values for gum were considered, the 90% CIs for $C_{\text{max}}$ and AUC$_{11-12}$ of lozenge (0.76-0.93 and 0.75-0.91, respectively) still fell within the enlarged 30% BAR (0.7-1.43), which may be considered acceptable for oral nicotine, due to its broad therapeutic range and self-titration behavior of users [27-29].

With respect to safety, 12 volunteers had a total of 40 AEs, which were all mild to moderate, with complete recovery. Six AEs (2 for lozenge and 4 for gum) were considered as drug-related: headache, salivation, hiccups, flatulence and throat irritation. No other clinically relevant abnormalities were observed, neither for cardiovascular parameters, nor for laboratory testing.

Dose proportionality between 1 and 2 mg lozenges and comparison with 4 mg gums at steady state

This study was performed to confirm the dose-concentration proportionality between 1 and 2 mg Nicotinell lozenges, and to compare the nicotine PK profile of lozenges with that of 4 mg nicotine gum. Overall trial design was comparable to the previous multiple-dose study, with intake of 12 doses of nicotine by 31 volunteers (1 dose per hour, 30 min of sucking or standardized chewing) and assessment of plasma nicotine PK parameters at steady state (successive blood draws after dose 12). Thirteen out of 31 (42%) of all trial participants had significant baseline plasma nicotine levels on two or three periods, but no differences were observed between the three treatment groups. Thus, these baseline levels were not taken into account, as they did not
influence the comparison between groups. The plateau concentration for plasma nicotine was reached before the 12th dose. With respect to dose-concentration proportionality between the 1 and 2 mg lozenge, an adjustment for the same dose (2 mg) was applied, and $C_{\text{max}}$ and $\text{AUC}_{11-12}$ were determined (Table 4). As expected, the 90% CIs of the ratio of $C_{\text{max}}$ and $\text{AUC}_{11-12}$ fell within the standard 20% BAR (0.80-1.25), thus demonstrating a linear dose-concentration relationship between the two strengths of nicotine lozenge (Figure 2). In addition, $t_{\text{max}}$ did not to differ significantly (Friedman ANOVA).

As bioequivalence between 1 mg lozenges and 2 mg gums had been shown (see above) and as 1 and 2 mg lozenges showed dose proportionality, one of the aims of this study was to compare 2 mg lozenge with 4 mg gum. With 2 mg lozenges, $C_{\text{max}}$ and $\text{AUC}_{11-12}$ were approximately 26% lower than with 4 mg gums. No bioequivalence was observed (Table 5).

Analysis of safety and tolerability was considered of particular value in this trial, as participants were treated with a wide range of nicotine doses under consistent conditions. Overall, no significant variations were reported in physical examination, vital signs, cardiovascular parameters or clinical laboratory tests. There were no serious or unexpected AEs. One subject was withdrawn due to vomiting when taking the 2 mg lozenges. The relationship was considered probable. Sixteen subjects reported a total of 29 AEs during the entire trial, which were all mild to moderate. The most frequent AEs assessed as at least possibly related to treatments were: hiccup (reported by 10 subjects, nine of which under the gums), throat irritation (two times with 2 mg lozenges and three times with gums), and nausea (ditto). Globally, more AEs were reported with the 4 mg gum than with the 1 or 2 mg lozenges, suggesting overall good tolerability of the latter formulation.
Safety in case of misuse of 1 mg lozenges

All clinical assessments performed in the PK trials, as well as reported AEs, suggested a favorable safety profile for Nicotinell® lozenges. However, in these trials one lozenge at a time was administered and subjects were sucking them slowly without concomitantly smoking. Yet, nicotine from oral formulations is not only taken up via the oral mucosa, but is also partially absorbed from the gastrointestinal tract [26]. To assess the safety in case of swallowing large quantities of 1 mg lozenges, an escalating-dose safety open study was performed: three groups (A, B, C), each including eight male or female subjects who were at least moderate smokers (≥10 cigarettes/day) received either 3, 6, or 12 Nicotinell 1 mg lozenges, to be swallowed at once with water. Smoking abstinence prior to dosing was not asked for and all of the volunteers (except one) had measurable levels of nicotine in plasma before lozenge intake. Blood was drawn until 48 h post-dose and plasma nicotine PK metrics were determined (Table 6). The highest mean concentration observed (20.5 ± 8.8 ng/ml) under these experimental conditions of misuse still fell largely within the range of plasma nicotine concentrations observed in active cigarette smokers (10-50 ng/ml) [14]. Of note, these observed concentrations were not corrected for the considerable baseline nicotine levels of the subjects.

The safety of lozenges when misused was also monitored through the assessment of the clinical status (including cardiovascular parameters), laboratory test results and occurrence of AEs. The different extents (according to dose) of nicotine absorption were not reflected in BP, HR, and ECG values, nor were any clinically significant changes in cardiac or laboratory parameters observed. No serious AEs were reported. Only one minor AE occurred in groups A and B (headache during 1 h). In group C, six volunteers reported transient stomach heaviness lasting for up to 1 h after
ingestion of the 12 lozenges. Gastric antral motor activity determined at 1 and 11 h post-dosing was identical to normal physiological values (3 ± 0.5 cycles/min). Gastric half clearance times at 1 and 11 h post-dosing were within the standard range (55 ± 15 min) for subjects receiving 3 or 6 lozenges, but not for those receiving 12 lozenges; the latter complained about stomach heaviness at 1 h post-dosing and displayed shortened gastric half clearance times (26 and 34 min). However, these AEs resolved spontaneously, and clearance half-times at 11 h post-dosing were again well within the standard range (49 and 62 min).

Efficacy of 1 mg lozenge for smoking cessation in phase 3 trials

In order to assess the clinical efficacy of 1 mg Nicotinell lozenge in helping smokers to quit smoking, two randomized placebo-controlled trials, involving approximately 900 subjects, were performed in France and the USA. For both trials, the demographic characteristics of enrolled subjects, including parameters related to past smoking history (years of smoking, number of cigarettes per day, exhaled CO, and urinary nicotine metabolite levels) were matched between groups (data not shown). The only important difference between the two studies was the level of patients’ cigarette dependence at inclusion (see Methods).

Briefly, the results for the primary efficacy criterion of the French trial at week 6 indicated a statistically significant increase in the number of subjects continuously abstinent from smoking with verum lozenges, with an odds ratio (OR) for abstinence of 1.72 [95% CI: 1.05-2.80] compared with placebo (Table 7). This result was in line with previously reported odds for quitting with NRT products in general [9] and a polacrilex lozenge formulation 2 mg in particular [16]. When the less selective, secondary efficacy criterion was applied (complete or partial smoking abstinence at week 6), the OR for abstinence with the lozenge was 2.18 [1.40-3.41], and statistically
significant differences (p <0.05) between lozenge and placebo in the percentage of abstinent smokers were found not only at week 6, but also for the follow-up visit at week 12 (Table 7 and Figure 4). At week 26, this difference was only significant for the subgroup of subjects previously smoking >20 cigarettes per day (data not shown). In addition, the evolution (compared to baseline) of the score for cessation-related withdrawal symptoms was determined, and increases proved to be less intense in trial subjects randomized to the lozenge group (p <0.001) than in those receiving placebo (Figure 5). Finally, there was no increased frequency of any side effects in the lozenge group and vital signs control did not reveal any relevant differences between the two treatment groups.

In the US trial, analysis for the primary efficacy criterion at week 6 also demonstrated a statistically significant superiority for lozenge vs. placebo in the number of quitters who remained continuously abstinent for 4 weeks (8.3% vs. 3.0%; p=0.02). The proportion of subjects continuously abstinent from week 2 through to week 12 was also significantly higher with lozenge (4.8%) than with placebo (1.3%; p=0.03) (Figure 6). However, the abstinence rates were lower than in the French trial, which might be due to patients’ higher dependence levels at inclusion. Withdrawal symptoms, assessed as total craving and total mood scores, were reduced in the verum group in comparison with the placebo group during the steady treatment period (up to week 6), with statistically significant differences in mean total craving scores at week 1 (p=0.03), and weeks 2 and 3 (p<0.01).

Overall, the use of Nicotinell 1 mg lozenges doubled the ratio of abstinence from smoking, with no increase in side effects compared with placebo. Of interest, the mean consumption in the US trial, which included more highly dependent smokers than the French trial, consisted of 12.9 nicotine lozenges/day during the steady
treatment phase (week 1-6), and decreased from 8.8 lozenges/day (week 7) to 3.3 lozenges/day (week 12) during the weaning phase. Corresponding amounts of lozenges/day in the French trial were 8.7 (week 1-6), 6.2 (week 7), and 1.9 (week 12). These numbers provided evidence for the self-titration behavior of smokers when using Nicotinell® 1 mg lozenge, with subjects adjusting their intake to their individual needs.
Discussion

This review presents PK data obtained during the clinical development process of 1 and 2 mg Nicotinell lozenges, which show that these formulations deliver significant amounts of nicotine, despite lower amounts of nicotine –base equivalents introduced in the lozenges. In addition, we present clinical data, which demonstrate that these lozenges are effective and safe for use by smokers wanting to quit smoking.

The high addictiveness of tobacco makes it difficult for smokers to quit without some form of additional help [32, 33]. Pharmaceutical NRT, i.e. the administration of purified nicotine under controlled regimens to smokers in order to help them to stop smoking cigarettes, aims at alleviating craving for nicotine and thereby prevents rapid relapse. Accordingly, over the last 20 years, a body of experimental evidence has demonstrated that the chances for motivated smokers to successfully quit were roughly doubled when NRT products were used [9]. Nicotine for NRT is available in a number of different pharmacological formulations, and lozenges are among the latest additions to the arsenal of NRT products [16, 22]. Oral nicotine formulations present both advantages and inconveniences directly related to this route of administration: their major drawback, as compared with transdermal patches, is that repeated intake of the drug is necessary to achieve sustained blood nicotine levels. On the contrary, the versatility of acute dosage forms allows abstinent smokers to address temporary craving episodes, and gives them the possibility of a behavioral response somehow similar to the previous cigarette-linked gestures.

Oral nicotine formulations are the treatment of choice when abstinent smokers want to keep an active control in situations that may trigger smoking relapse, e.g. before stressful meetings or social events [8, 34]. While worldwide the gum formulations are
the most common oral NRT products, a number of disadvantages might render people reluctant to use them: incompatibility with dental works or temporomandibular joint pain, cultural or social acceptance and occurrence of AEs (e.g. hiccup or throat irritation) [35]. In this respect, lozenges present a valuable alternative as their use is more discrete and aesthetic.

Nicotine is best absorbed when it is in its non-ionized form, which rapidly crosses biomembranes. Accordingly, in the development of 1 and 2 mg Nicotinell lozenges, particular attention has been paid to optimization of the alkalizing resin to obtain optimal nicotine release and absorption. The new formulations for lozenges were compared to 2 and 4 mg nicotine polacrilex gums (Nicorette®), which are pharmacologically well-characterized and were the first oral NRT product on the market [15, 26, 36, 37].

Comparison of PK parameters after a single dose of lozenge or gum showed that the amount of nicotine absorbed through 1 mg Nicotinell lozenges is similar to that obtained via 2 mg polacrilex gums, and that both formulations have comparable kinetics. In addition, dose-concentration proportionality between 1 and 2 mg Nicotinell® lozenges was evident from PK metrics, with a net doubling of $C_{\text{max}}$ and AUC achieved with the 2 mg formulation compared to the 1 mg formulation. The discrepancy in gross nicotine delivery between Nicotinell 1 mg lozenges and polacrilex 2 mg gums in the single-dose study is only apparent and was not found in the latter studies, when the sucking pattern was adapted: lozenges are designed to be completely sucked out, whereas gums are known to retain a significant amount of nicotine within the resin (28% and 47% of total nicotine content, respectively for 4 mg and 2 mg gums, approximately 1 mg nicotine) [25]. Besides, variations among
individuals, probably due to differences in mastication intensity, chewing techniques or oral pH could explain some of the differences [26].

Comparable absorption of nicotine from 1 mg lozenges and 2 mg gums was confirmed in the first multiple dose trial, performed to compare the PK profile of both formulations under conditions close to real use of NRT products. At steady state, all assessed PK parameters were similar and formal bioequivalence using the standard 20% BAR was demonstrated for $C_{\text{max}}$ and AUC. In the second multiple dose trial the dose-concentration proportionality between Nicotinell® 1 and 2 mg lozenges was confirmed, with 2 mg lozenges inducing plasma concentrations intermediate between those obtained with 1 mg lozenges and 4 mg polacrilex gums.

Accordingly, the systemic exposure to nicotine with Nicotinell lozenges and with Nicorette gums, under conditions reflecting the intended use, could be ranked as follows: 4 mg polacrilex gums > 2 mg Nicotinell lozenge > 1 mg Nicotinell lozenge = 2 mg polacrilex gum.

The criteria applied to evaluate bioequivalence between different NRT products can give rise to discussion. Indeed, even when the standard 20% BAR does not argue in favor of bioequivalence, the enlarged 30% BAR is relevant to assess bioequivalence between two oral NRT formulations. This reasoning is based on some peculiar behavior encountered in smokers: smokers regulate their intake of nicotine by the number of cigarettes they smoke and their inhaling mode. They achieve the desired effects and minimize withdrawal symptoms by adjusting an individual “optimal” blood level of nicotine [27]. Similarly, the intake of NRT oral or nasal products is subject to self-titration: clinical studies showed that the use of nicotine gums or nasal spray followed a principle of self-titration similar to that observed with cigarettes, with an ad-libitum schedule resulting in more constant blood levels than a fixed
schedule [28, 29]. It can reasonably be assumed that nicotine self-titration behavior is found with all cessation products administered in multiple doses per day and favors individual adjustment of the dose to achieve the desired effect. In this respect, bioequivalence using the enlarged 30% BAR was achieved in the multiple-dose study comparing 1 mg lozenge with 2 mg gum, even when no adjustment for increasing nicotine release from the gum with time was applied (90% CI [lozenge / gum] for $C_{\text{max}}$: 0.76-0.93; for $\text{AUC}_{11-12}$: 0.75-0.91).

The safety of 1 and 2 mg Nicotinell lozenges can be assessed based on the observations of the 70 healthy adult male smokers enrolled in the PK trials. In this study population exposed to single or multiple doses of lozenges, no serious or unexpected AEs and no changes in physical examination, vital signs, cardiovascular parameters and laboratory values were observed. Reported AEs were mild or (at worst) moderate in intensity, transient and completely reversible. This good tolerability of lozenges is in line with safety results reported in previous clinical trials with nicotine polacrilex lozenges [16, 22, 30]. Even during the complementary safety trial, with subjects swallowing up to 12 lozenges at once, no serious or lasting AEs were reported and the overall tolerability was rated as excellent. Finally, the data from the two large phase 3 efficacy trials further confirmed the safety profile of the nicotine lozenges, as there were no relevant differences in AE frequency or nature between placebo and verum groups. In addition, the vast majority of the reported AEs could also be attributed to the effects of abrupt smoking cessation.

The efficacy trials were designed to provide sufficient power for the statistical analysis of the primary efficacy criterion: controlled continuous smoking abstinence during the 28 days preceding the visit scheduled at week 6. This primary efficacy criterion was severe, as it obliged subjects to stop smoking completely before the end
of the second week of treatment, compared with 3-week to 12-month reported for some nicotine gum trials [9]. However, the short treatment period seems to be more in line with “real world use” by consumers [31]. In addition, the weaning phase of 6 weeks (from week 7 to 12, after which no more lozenges were supplied) was also relatively short compared with some published nicotine gum trials, and subjects starting to smoke again were excluded from follow-up, regardless of their ensuing performance. These particularities must be remembered when interpreting the efficacy results. Further, in both trials, no specific behavioral counseling or support was provided to the studied populations. Notwithstanding these facts, the statistically significant differences in abstinence rates as well as the odds for successful quitting with lozenge vs. placebo did underscore the efficacy of 1 mg nicotine lozenge as a smoking cessation aid.

Comparative analysis of PK metrics of the 1 and 2 mg lozenge showed that at steady state $C_{\text{max}}$ was approximately 11 and 23 ng/ml, respectively. Notably, these levels are on the lower end of the range of blood nicotine levels (10-50 ng/ml) observed in smokers at steady state. As nicotine underdosing during smoking cessation is generally considered to increase the risk for failure in nicotine dependent patients [13, 31], the 2 mg Nicotinell lozenge may provide increased efficacy for heavily to very heavily dependent smokers, whereas the 1 mg dose may fulfill the needs of light to moderate dependent smokers. Considering a possible abuse potential of the lozenges, which is inherent to all NRT products administered in multiple doses per day, it should be noted that in the French efficacy trial urinary cotinine levels decreased not only in the population of abstinent subjects receiving placebo, but also in the population receiving 1 mg lozenges, thus clearly indicating that quitters do not overdose the product.
Conclusions

The data presented in this review demonstrate the high nicotine bioavailability, the good safety and the proven efficacy of Nicotinell lozenges. Namely, at nominal equivalent doses 1 and 2 mg Nicotinell lozenges were shown to deliver comparatively higher amounts of bioavailable nicotine than the widely used nicotine polacrilex gums. All AEs observed during the clinical development were mild or moderate in severity, transient and completely reversible. With respect to efficacy in smoking cessation, significantly higher abstinence rates (4-week continuous abstinence after six weeks of treatment) were achieved with lozenge compared to placebo. Therefore, Nicotinell lozenges are a valuable addition to the therapeutic armamentarium available for smoking cessation.
Competing interests

J.-L. Kienzler and A. Callens are employees of Novartis Consumer Health S.A. which produce and distribute nicotine replacement products. All research trials were funded by Novartis Consumer Health.
Authors' contributions

B. Dautzenberg was the principal investigator of the French phase 3 efficacy trial. M. Nides participated to the Novartis Consumer Heath smoking cessation activities in the US. J.-L. Kienzler and A. Callens supervised and coordinated the clinical development of the Nicotinell® lozenges. All authors read and approved the final manuscript.
Acknowledgements

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The authors also wish to thank all the people involved in the conduct of the trials presented in this review, especially the investigators and CRO staff members.
References


Figures

Figure 1 - Nicotine plasma concentration after repeated intake (24 subjects)

Nicotine plasma concentrations were determined in this multiple-dose bioequivalence trial with 24 volunteers from blood samples drawn before administration of each single dose (unconnected data points). Consecutive blood samples (connected data points) were drawn after administration of dose 1 (t=0) and dose 12 (t=11 h). The insert shows a blood nicotine peak after dosing at steady state obtained with blood draws after dose 12 (11-12 h).
Figure 2 - Proportionality of nicotine lozenges with respect to nicotine plasma concentrations (31 subjects)

Nicotine plasma concentrations were determined from blood samples of 31 volunteers drawn before hourly administration 1 or 2 mg nicotine lozenge (unconnected data points). Consecutive blood samples (connected data points) were drawn after administration of dose 12 (t=11 h), and the derived data points are connected. Plasma concentrations obtained with 1 mg lozenges were doubled for ease of comparison.
Figure 3 - Nicotine plasma concentration after repeated intake of nicotine lozenges or gums (31 subjects)

Nicotine plasma concentrations were determined from blood samples of 31 volunteers drawn before hourly administration 1 or 2 mg nicotine lozenge or 4 mg nicotine gums (unconnected data points). Consecutive blood samples (connected data points) were drawn after administration of dose 12 (t=11 h).
Figure 4 - Smoking cessation success rates among users of 1 mg nicotine lozenges (moderate dependent patients) (adopted from [17])

The rate of fully (no cigarettes) or partially (≤1 cigarette/day and ≤7 cigarettes/week) abstinent subjects using 1 mg nicotine lozenges for abrupt quitting over the first 6 months of the French efficacy trial.
Figure 5 - Withdrawal symptom score (change vs. baseline) among users of 1 mg nicotine lozenges (adopted from [18])
Figure 6 - Smoking cessation success rates among users of 1 mg nicotine lozenges (highly dependent patients)

The rate of completely abstinent subjects using 1 mg nicotine lozenges for abrupt quitting over the first 6 months of the U.S. efficacy trial.
### Tables

#### Table 1 - Ethic comittee approvals

<table>
<thead>
<tr>
<th>Study</th>
<th>Ethical Comitee</th>
</tr>
</thead>
<tbody>
<tr>
<td>single-dose, comparing 1 and 2 mg lozenges with 2 mg gum</td>
<td>CCPPRB de Franche-Comté, France</td>
</tr>
<tr>
<td>multiple-dose, comparing 1 mg lozenge with 2 mg gum</td>
<td></td>
</tr>
<tr>
<td>multiple-dose, comparing 1 and 2 mg lozenges with 4 mg gum</td>
<td>CCPPRB of the Hôtel-Dieu Hospital (Lyon – France))</td>
</tr>
<tr>
<td>safety assessment of 1 mg lozenge after swallowing</td>
<td>CREC Regipharm (Brussels – Belgium)</td>
</tr>
<tr>
<td>French efficacy trial</td>
<td>CCPPRB of the Pitié-Salpêtrière Hospital (Paris – France)</td>
</tr>
<tr>
<td>US efficacy trial</td>
<td>IRB at Research Testing Laboratories, Inc. (Great Neck, NY, USA)</td>
</tr>
</tbody>
</table>
Table 2 - PK parameters of nicotine in plasma after intake of a single dose of lozenge or gum (mean ± SD; n=9)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Formulation</th>
<th>Nicotinell® lozenge</th>
<th>Nicorette® gum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Amount of nicotine released after 30 min (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[% of minimal content]</td>
<td>0.67 ± 0.14</td>
<td>1.39 ± 0.28</td>
<td>0.81 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>[67%]</td>
<td>[67%]</td>
<td>[42%]</td>
</tr>
<tr>
<td>observed C&lt;sub&gt;max&lt;/sub&gt; (ng/ml) [adjusted]&lt;sup&gt;†‡&lt;/sup&gt;</td>
<td>2.3 ± 0.8</td>
<td>4.8 ± 1.4</td>
<td>2.9 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>[3.5 ± 1.1]&lt;sup&gt;†&lt;/sup&gt;</td>
<td>[7.0 ± 1.7]&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h) [median (range)]</td>
<td>1.1 ± 0.7</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>[0.8 (0.8-3.0)]</td>
<td>[0.8 (0.6-1.1)]</td>
<td>[0.8 (0.5-1.0)]</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>2.7 ± 0.7</td>
<td>2.8 ± 0.7</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (h·ng/ml)</td>
<td>8.3 ± 2.5</td>
<td>15.8 ± 4.1</td>
<td>10.6 ± 4.4</td>
</tr>
<tr>
<td>observed AUC&lt;sub&gt;0-t&lt;/sub&gt; (h·ng/ml) [adjusted]&lt;sup&gt;†‡&lt;/sup&gt;</td>
<td>10.7 ± 3.1</td>
<td>20.0 ± 5.9</td>
<td>13.8 ± 5.6</td>
</tr>
<tr>
<td></td>
<td>[16.5 ± 4.6]&lt;sup&gt;†&lt;/sup&gt;</td>
<td>[30.1 ± 9.7]&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

†: Since in this trial nicotine lozenges were not completely dissolved after 30 min of sucking, an adjustment was made for nicotine delivery by a full 1 mg dose.
‡: Adjustment for nicotine delivery by a full 2 mg dose.


Table 3 - PK parameters of nicotine in plasma at steady state after 12 hourly doses‡ of 1 mg lozenge or 2 mg gum (mean ± SD; n=24)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Nicotinell® lozenge 1 mg</th>
<th>Nicorette® gum 2 mg‡</th>
<th>90% CI (lozenge / gum)◊</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>10.6 ± 2.9</td>
<td>11.4 ± 3.8</td>
<td>0.86-1.04</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/ml)</td>
<td>8.1 ± 2.4</td>
<td>9.3 ± 3.4</td>
<td>ND</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h) [range]</td>
<td>0.54 ± 0.21 [0.00-0.77]</td>
<td>0.47 ± 0.19 [0.20-0.95]</td>
<td>ND</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>3.6 ± 1.2</td>
<td>3.2 ± 0.9</td>
<td>ND</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;11-12&lt;/sub&gt; (h·ng/ml)</td>
<td>9.2 ± 2.6</td>
<td>10.2 ± 3.4</td>
<td>0.84-1.01</td>
</tr>
</tbody>
</table>

Initial nicotine concentrations in plasma were 1.1 ng/ml (range: 0.0-6.5) with lozenge and 0.9 ng/ml (0.0-5.1) gum, reflecting volunteers’ heavy smoking habits (≥20 cigarettes per day). Correction for initial nicotine concentrations did not modify the results and thus was not retained. ND: not determined.

†: PK parameters were determined from blood samples drawn after dose 12 (t=11 h) until t=23 h.

‡: a dose adjustment of the raw data was done for a last standard dose of 1 mg nicotine delivery from the gum.

◊: Standard 90% CI for the expected mean ratio was derived from ANOVA for continuous parameters and compared to standard 20% BAR (0.80-1.25).
Table 4 - Steady state† plasma nicotine PK parameters after intake of 1 or 2 mg lozenges to determine dose-concentration proportionality (mean ± SD; n=31)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Nicotinell® lozenge 1 mg</th>
<th>Nicotinell® lozenge 2 mg</th>
<th>90% CI (2 mg / 1 mg)#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>observed</td>
<td>adj. to 2 mg‡</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>11.0 ± 4.9</td>
<td>22.0 ± 9.8</td>
<td>22.5 ± 7.0</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h) Median [range]</td>
<td>0.5 [0.25-1.00]</td>
<td>-</td>
<td>0.5 [0.25-1.02]</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;11-12&lt;/sub&gt; (h·ng/ml)</td>
<td>9.7 ± 3.9</td>
<td>19.3 ± 7.8</td>
<td>20.2 ± 6.8</td>
</tr>
</tbody>
</table>

NS: not significant.
†: PK parameters were determined from blood samples drawn after dose 12 (t=11 h) until t=23 h.
‡: Experimental values (plasma nicotine concentrations) observed with 1 mg lozenge were adjusted to a hypothetical 2 mg dose before calculation of PK parameters.
#: Standard 90% CI for the expected mean ratio was derived from ANOVA for continuous parameters and compared to standard 20% BAR (0.80-1.25). F: relative bioavailability ratio.
Table 5 - PK parameters of nicotine in plasma at steady state after 12 hourly doses\(^\dagger\) of 2 mg lozenge or 4 mg gum (mean ± SD; n=31)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Nicotinell(^g) lozenge</th>
<th>Nicorette(^g) gum</th>
<th>90% CI (lozenge / gum)(^\ddagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg</td>
<td>4 mg</td>
<td></td>
</tr>
<tr>
<td>(C_{\text{max}}) (ng/ml)</td>
<td>22.5 ± 7.0</td>
<td>30.5 ± 12.8</td>
<td>0.69-0.89 (F=0.78)</td>
</tr>
<tr>
<td>(t_{\text{max}}) (h)</td>
<td>Median [range]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 [0.25-1.02]</td>
<td>0.5 [0.25-1.00]</td>
<td>NS (Friedman ANOVA)</td>
</tr>
<tr>
<td>(AUC_{11-12}) (h·ng/ml)</td>
<td>20.2 ± 6.8</td>
<td>27.5 ± 11.4</td>
<td>0.68-0.88 (F=0.77)</td>
</tr>
</tbody>
</table>

NS: not significant.
\(\dagger\): PK parameters were determined from blood samples drawn after dose 12 (t=11 h) until t=23 h.
\(\ddagger\): Standard 90% CI for the expected mean ratio (test / reference = lozenge / gum) was derived from ANOVA for continuous parameters and compared to standard 20% BAR (0.80-1.25) and enlarged 30% BAR (0.7-1.43). F: relative bioavailability ratio.
Table 6 - PK parameters of nicotine in plasma after swallowing without sucking of increasing numbers of 1 mg lozenge (mean ± SD; n=8 per group)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 lozenges</td>
<td>6 lozenges</td>
<td>12 lozenges</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>8.2 ± 7.6</td>
<td>16.9 ± 11.8</td>
<td>20.5 ± 8.8</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.7 ± 2.8</td>
<td>2.8 ± 2.0</td>
<td>2.2 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;10min-12h&lt;/sub&gt; (h.ng/ml)</td>
<td>37.0 ± 27.2</td>
<td>84.9 ± 48.9</td>
<td>103.1 ± 58.6</td>
<td></td>
</tr>
</tbody>
</table>

PK parameters were not corrected for baseline plasma nicotine levels.
Table 7 - Primary and secondary efficacy criteria: complete or partial abstinence during the 28 days preceding the 6-week visit (adopted from [17])

<table>
<thead>
<tr>
<th>Statistical metrics</th>
<th>Group</th>
<th>Nicotinell® lozenge 1 mg (n=211)</th>
<th>Placebo (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully abstinent (%)</td>
<td></td>
<td>48 (23%)</td>
<td>32 (14%)</td>
</tr>
<tr>
<td>OR [95% CI]</td>
<td></td>
<td>1.72 [1.05-2.80]</td>
<td></td>
</tr>
<tr>
<td>Statistical significance</td>
<td></td>
<td>p=0.03</td>
<td></td>
</tr>
<tr>
<td>Fully or partially abstinent (%)</td>
<td></td>
<td>68 (32%)</td>
<td>39 (18%)</td>
</tr>
<tr>
<td>OR [95% CI]</td>
<td></td>
<td>2.18 [1.40-3.41]</td>
<td></td>
</tr>
<tr>
<td>Statistical significance</td>
<td></td>
<td>p=0.001</td>
<td></td>
</tr>
</tbody>
</table>

Fully abstinent = subjects declaring not to smoke (controlled by an exhaled-breath CO <10 ppm). Partially abstinent = subjects smoking ≤1 cigarette/day and ≤7 cigarettes/week, and with an exhaled-breath CO <10 ppm.
Figure 1

Nicotine plasma concentration (ng/ml\(^{-1}\))

- Gum 2 mg
- Lozenge 1 mg

Time (hours)

0 2 4 6 8 10 12 14 16 18 20 22 24
Figure 2

Graph showing nicotine plasma concentration (ng.ml\(^{-1}\)) over time (hours) for Lozenge 2 mg and 2x Lozenge 1 mg.

- Lozenge 2 mg
- 2x Lozenge 1 mg

Time points indicated by arrows on the x-axis (0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours).
Figure 3

- Gum 4 mg
- Lozenge 2 mg
- Lozenge 1 mg

Observation time (hours)
Observed nicotine plasma concentration (µg/l)
Figure 4

Success rate vs. delay since smoking cessation (weeks).

- **Lozenge 1mg**
  - 0% at 0 weeks
  - 10% at 6 weeks
  - 19% at 12 weeks
  - 15% at 18 weeks
  - p = 0.001

- **Placebo**
  - 9% at 0 weeks
  - 10% at 6 weeks
  - 18% at 12 weeks
  - 15% at 18 weeks
  - p =

Legend:
- **Steady treatment**
- **Weaning**
- **No treatment**
Figure 5

Withdrawal symptom score

Week 1 Week 2 Week 4 Week 6

Lozenge 1mg
Placebo

p<0.001
Figure 6

Comparison of success rates between NL 1mg (n = 230) and Placebo (n = 230) after smoking cessation.

- NL 1mg (n = 230)
- Placebo (n = 230)

Success rate and delay since smoking cessation (weeks).

Significance levels:
- p = 0.02
- p = 0.03
- p = 0.06