SIGNATURES

An open-label, randomized, two-way cross-over bioequivalence study in healthy smokers of Zonnic® Cool mint 1.5 mg medicated chewing-gum versus Nicorette® 2 mg nicotine chewing gum Classic flavour

Study Number: TIO 09-01

I have read this report and confirm that it to the best of my knowledge accurately describes the conduct and results of the study.

Principal Investigator:

June 15, 2009

Elsy-Britt Schildt, MD
Dept. of Oncology, University Hospital Lund
Lund, Sweden

Date

Sponsor's Representative:

June 15, 2009

Anders Axelsson, M.Sc. Pharm
Niconovum AB
Järnvägsgatan 13
SE-252 24 Helsingborg, Sweden

Date

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SYNOPSIS

Name of Sponsor/Company: Niconovum AB	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF THE DOSSIER Volume: Page: **Study No.:** TIO 09-01	*For National Authority Use only*
Name of Finished Product: Zonnic® Cool mint 1.5 mg medicated chewing-gum		
Name of Active Ingredient: Nicotine		

Title of Study: An open-label, randomized, two-way cross-over bioequivalence study in healthy smokers of Zonnic® Cool mint 1.5 mg medicated chewing-gum versus Nicorette® 2 mg nicotine chewing gum Classic flavour

Investigators: Dr Elsy-Britt Schildt, MD, Dept. of Oncology, University Hospital Lund, SE-221 85 Lund, Sweden and Karl Olov Fagerström, PhD, Smokers Information Centre, Berga Allé 1, SE- 25452 Helsingborg, Sweden

Study Centre: Smokers Information Centre, Helsingborg, Sweden

Publication: Not applicable.

Studied period: 04-Feb-2009 - 05-Mar-2009	**Phase of development:** IV

Objectives:

Primary objective:

- To estimate the nicotine plasma concentrations following a single dose of Zonnic® Cool mint 1.5 mg medicated chewing-gum in comparison to Nicorette® 2 mg nicotine chewing gum Classic flavour when the Zonnic product is chewed for 10 min and the Nicorette product for 30 min.

Secondary objectives:

- To assess craving for tobacco as a function of time since administration of study product and plasma concentration
- To estimate subjective time to effect and preference (Preference was not recorded.)
- To compare the increases in nicotine plasma levels at 3, 6, 10 and 20 min resulting from the respective products.

Other objectives:

Relationship between dose and plasma concentrations of nicotine. Population pharmacokinetics (PK).

Methodology:

The study was conducted as a randomised, open, two-period cross-over trial where the treatments, Zonnic® Cool mint 1.5 mg medicated chewing-gum ("Zonnic 1.5 mg") and Nicorette® 2 mg nicotine chewing gum Classic flavour ("Nicorette 2 mg"), were given to the subjects in random order at two investigation visits (treatment periods A and B). The treatment periods were separated by a wash-out period of at least 1 day. All subjects were to receive both treatments as single dose administrations. The products studied were:

Treatment period A: Zonnic® Cool mint 1.5 mg medicated chewing-gum

Treatment period B: Nicorette® 2 mg nicotine chewing gum Classic flavour

At the first visit eligibility to participate in the study was checked and the subject was given information about the study procedures and signed the informed consent form before demographic data, body height and weight, supine blood pressure (BP) and heart rate (HR), concurrent diseases/symptoms and concomitant medication were documented.

Measurement of exhaled carbon monoxide (ECO) was performed before administration of investigational drugs at each visit to confirm that the subject had abstained from smoking. Levels of ECO up to 10 ppm were considered compatible with abstinence. Concomitant medication was recorded. An intravenous (IV) cannula was administered for the blood sampling and blood was drawn at baseline (=0 min).

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Name of Active Ingredient: Nicotine		

Administration of investigational drug occurred at time point 0 min. Subjects were given single dose administrations of Zonnic® Cool mint 1.5 mg medicated chewing-gum (Treatment period A) and Nicorette® 2 mg nicotine chewing gum Classic flavour (Treatment period B) at two occasions separated by at least one day. Zonnic 1.5 mg was chewed over 10 min while Nicorette 2 mg was chewed over 30 min using a metronome to standardise the chewing rate, one chew every two seconds.

Blood (5 ml) was drawn at baseline (=0 min) and then at 3, 6, 10, 20, 30, 45, 60 min and 1.5, 2, 3, 4, 5 and 6 h after drug administration for PK analysis of nicotine levels. Supine BP and HR were measured at the end of each study day. An adverse event (AE) interview (open questioning) was conducted at the end of each study day.

At the time points 0, 3, 6, 10, 20 and 30 min, the subjects rated their craving on a visual analogue scale (VAS) on a line of 100 mm where one end was anchored as “no craving” and the other “extreme craving”. The subjects saw their previous ratings which is standard practice in studies of tobacco abstinence symptoms because it is easier for subjects to determine the degree of craving relative to past ratings and the variation thus decreases.

Number of patients (planned and analysed):

	Zonnic® Cool mint 1.5 mg medicated chewing-gum	Nicorette 2 mg nicotine chewing gum Classic flavour
No. planned:	24	24
No. analysed for primary PK variable:	24	24
No. analysed for safety:	24	24
No. completed:	24	24

Diagnosis and main criteria for inclusion

- Consent to participate voluntarily and sign informed consent prior to any study procedure
- Healthy male and female, age 18 through 60 years
- Willing and able to chew nicotine chewing-gum
- Willing and able to comply with the study-specific procedures
- Smoker of ≥10 cigarettes/day.

Test product, dose and mode of administration, batch number:
Single dose administrations of Zonnic® Cool mint 1.5 mg medicated chewing-gum. One piece was chewed over 10 min using a metronome to standardise the chewing rate, one chew every two seconds.
Batch No.: 08E50

Duration of treatment:
Two investigation days separated by a wash-out period of at least 1 day.

Reference therapy, dose and mode of administration, batch number:
Single dose administrations of Nicorette® 2 mg nicotine chewing gum Classic flavour. One piece was chewed over 30 min using a metronome to standardise the chewing rate, one chew every two seconds.
Batch No.: KC179A

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Name of Finished Product: Zonnic® Cool mint 1.5 mg medicated chewing-gum		
Name of Active Ingredient: Nicotine		

Criteria for evaluation:

Efficacy

- Area under the plasma concentration versus time curve from 0 to 6 hours (AUC_{0-6h}) based on baseline-corrected and uncorrected values in the ITT population
- Maximal plasma concentration (C_{max})
- Time to maximal plasma concentration (T_{max})
- Area under curve from 0 h to infinity ($AUC_{(0-\infty)}$)
- Area under curve from 0h to 24h ($AUC_{(0-24h)}$) (Not performed as this was not relevant due to the short half-life.)
- % extrapol ($AUC_{(0-\infty)}$ - $AUC_{(0-24h)}$ / $AUC_{(0-\infty)}$) (Not performed as this was not relevant due to the short half-life.)
- Craving for tobacco as a function of time (0. 3, 6, 10, 20 and 30 min) since administration of study product, assessed by a VAS scale (0-100 mm)
- Subjective time to effect.

Safety

-Adverse events (AEs)

-Heart rate (HR) and supine blood pressure (BP).

Statistical methods: The bioequivalence between Zonnic® Cool mint 1.5 mg medicated chewing-gum and Nicorette® 2 mg nicotine chewing gum Classic flavour was estimated by calculating the geometric mean and the 90% confidence interval (CI) for the quotients of C_{max}, $_cAUC_{0-6h}$ and $_cAUC_{inf}$. Bioequivalence was to be declared if the quotients were contained within the limits 0.8–1.25. Additional analyses using logarithmically transformed data were performed because bioequivalence is considered to be present when the quotients of the AUC_{0-t} and C_{max} of the logarithmically transformed data from the compared drugs are within the 0.8 - 1.25 range. The differences between Zonnic 1.5 mg and Nicorette 2 mg are shown descriptively. Adverse events, tolerability self-reports and heart rate are reported descriptively.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The mean $_cC_{max}$ was lower for Zonnic 1.5 mg (3.35 ng/ml; SD: 1.39 ng/ml) than for Nicorette 2 mg (5.15 ng/ml; SD: 1.63 ng/ml). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -1.81 ng/ml; 95% CI: -2.63 to -0.99) was statistically significant (two-tailed t-test: p<0.001; Wilcoxon Signed ranks test: p=0.001). The mean quotient of $_cC_{max}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.70 with a 90% CI of 0.59 to 0.82.

The mean $_cAUC_{0-6h}$ was lower for Zonnic 1.5 mg (6.91 ng x h/ml; SD: 2.46 ng x h/ml) than for Nicorette 2 mg (10.37 ng x h/ml; SD: 3.96 ng x h/ml). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -3.46 ng x h/ml; 95% CI: -5.40 to -1.51) was statistically significant (two-tailed t-test: p=0.002; Wilcoxon Signed ranks test: p=0.001). The mean quotient of $_cAUC_{0-6h}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.78 with a 90% CI of 0.61 to 0.96.

Also the mean $_cAUC_{inf}$ was lower for Zonnic 1.5 mg (7.45 ng x h/ml; SD: 2.60 ng x h/ml) than for Nicorette 2 mg (10.99 ng x h/ml; SD: 4.16 ng x h/ml). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -3.54 ng x h/ml; 95% CI: -5.62 to -1.47) was statistically significant (two-tailed t-test: p=0.003; Wilcoxon Signed ranks test: p=0.001). The mean quotient of $_cAUC_{inf}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.78 with a 90% CI of 0.63 to 0.92.

Based on non-transformed PK data, bioequivalence was not achieved as the quotients for $_cC_{max}$, $_cAUC_{0-6h}$ and $_cAUC_{inf}$ were not within the 0.8-1.25 limits. Because bioequivalence is generally considered to be present when the quotients of the AUC_{0-t} and C_{max} of the logarithmically transformed data from the compared drugs are within the 0.8 - 1.25 range, additional analyses using logarithmically transformed data were performed. Based on uncorrected log-

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Name of Finished Product: Zonnic® Cool mint 1.5 mg medicated chewing-gum		
Name of Active Ingredient: Nicotine		

transformed data, AUC_{0-6h} (quotient: 0.91), C_{max} (quotient: 0.81) and AUC_{inf} (quotient: 0.95) all met the bioequivalence criteria. Based on baseline-corrected log-transformed data, AUC_{0-6h} (quotient: 0.86) and AUC_{inf} (quotient: 0.86) but not C_{max} (quotient: 0.73) met the bioequivalence criteria.

The mean T_{max} was similar for Zonnic 1.5 mg (0.73 h, i.e. 44 min) and Nicorette 2 mg (0.69 h, i.e. 42 min). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: 0.035 h, i.e. 2 min) was not statistically significant (two-tailed t-test: p=0.80; Wilcoxon Signed ranks test: p=0.677).

The mean subjective time to effect measured on a VAS scale was shorter for Zonnic 1.5 mg (68.8 sec; SD: 35.8 sec) than for Nicorette 2 mg (135 sec; SD: 174 sec). The median subjective time to effect was 17.5 sec shorter with Zonnic 1.5 mg than with Nicorette 2 mg. Based on negative ranks, the time to effect was statistically significantly shorter for Zonnic 1.5 mg with a p-value of 0.005 in the two-tailed Wilcoxon Signed Ranks test.

The highest mean craving score was observed at 5 minutes before administration of Zonnic 1.5 mg (57.9 mm; range: 8 mm-98 mm) or Nicorette 2 mg (59.5 mm; range: 5 mm-99 mm). Gradually lower mean craving scores were then reported with the lowest values at the last time point, 30 min, when the score was 21.5 mm (range: 1 mm-73 mm) during the Zonnic 1.5 mg period and 21.7 mm (range: 0 mm-82 mm) during the Nicorette 2 mg period. Minimum craving during the 30-minute period was reported by 10 of 24 subjects (42%) receiving Zonnic 1.5 mg and 9 of 24 subjects receiving Nicorette 2 mg. There was no statistically significant difference in craving tobacco between Zonnic 1.5 mg and Nicorette 2 mg at any given time point during the first 30 minutes of the study period. There was a statistically significant negative correlation between tobacco craving and plasma nicotine level, i.e. craving decreased with increasing nicotine levels.

The mean residual nicotine amount in the chewing-gum after chewing was lower for Zonnic 1.5 mg (0.088 mg; SD: 0.025 mg) than for Nicorette 2 mg (0.19 mg; SD: 0.86 mg).

SAFETY RESULTS:
All enrolled 24 subjects completed both treatment periods. No AEs were reported in this study and no safety concerns were identified.

CONCLUSION:
The mean $_cC_{max}$ was lower for Zonnic 1.5 mg (3.3 ng/ml) than for Nicorette 2 mg (5.2 ng/ml). The mean quotient of $_cC_{max}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.701 with a 90% CI of 0.587 to 0.815. Also the mean $_cAUC_{0-6h}$ and $_cAUC_{inf}$ were lower for Zonnic 1.5 mg than for Nicorette 2 mg with a mean quotient (Zonnic 1.5 mg divided by Nicorette 2 mg) of 0.782 and 0.779, respectively.

Because bioequivalence is generally considered to be present when the quotients of the AUC_{0-t} and C_{max} of the logarithmically transformed data from the compared drugs are within the 0.8 - 1.25 range, additional analyses using logarithmically transformed data were performed. Based on uncorrected log-transformed data, AUC_{0-6h} (quotient: 0.91), C_{max} (quotient: 0.81) and AUC_{inf} (quotient: 0.95) all met the bioequivalence criteria. Based on baseline-corrected data, AUC_{0-6h} (quotient: 0.86) and AUC_{inf} (quotient: 0.86) but not C_{max} (quotient: 0.73) met the bioequivalence criteria.

The mean T_{max} was similar for Zonnic 1.5 mg (44 min) and Nicorette 2 mg (42 min). Also the mean elimination rate and the mean half-life were similar for Zonnic 1.5 mg and Nicorette 2 mg.

The mean subjective time to effect measured on a VAS scale was statistically significantly shorter for Zonnic 1.5 mg (68.8 sec) than for Nicorette 2 mg (135 sec) with a p-value of 0.005 in the two-tailed Wilcoxon Signed Ranks test

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Name of Finished Product: Zonnic® Cool mint 1.5 mg medicated chewing-gum		
Name of Active Ingredient: Nicotine		
and a p-value of 0.007 in the two-tailed exact significance test. No AEs were reported in this study and no safety concerns were identified.		
Date of the report: 14-Jun 2009		

3. TABLE OF CONTENTS

16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

16.1.11 Publications based on the study

16.1.12 Important publications referenced in the report

16.2 PATIENT DATA LISTINGS

16.2.1 Discontinued patients

16.2.2 Protocol deviations

16.2.3 Patients excluded from the efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data (if available)

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each patient)

16.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities

16.3 CASE REPORT FORMS

16.3.1 CRFs of deaths, other serious adverse events and withdrawals for AE

16.3.2 Other CRFs submitted

16.4 INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of Variance
$AUC_{0\text{-}6h}$	Area under the plasma concentration versus time curve from 0 h to 6 h
AUC_{inf}	Area under the plasma concentration versus time curve from 0 h to infinity
$_cAUC_{0\text{-}6h}$	$AUC_{0\text{-}6h}$ corrected for baseline nicotine plasma concentration
$_cAUC_{inf}$	AUC_{inf} corrected for baseline nicotine plasma concentration
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
C_{max}	Maximum Concentration
CRF	Case Report Form
df	Degrees of Freedom
ECO	Exhaled Carbon Monoxide
GCP	Good Clinical Practice
HR	Heart Rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ITT	Intention to Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Product Agency
Nicorette 2 mg	Nicorette® 2 mg nicotine chewing gum Classic flavour
NRT	Nicotine Replacement Therapy
OTC	Over-the-counter
PK	Pharmacokinetics
PP	Per Protocol
SAE	Serious Adverse Event
SAER	Serious Adverse Event Report
SD	Standard Deviation
T_{max}	Time of C_{max}
VAS	Visual Analogue Scale
Zonnic 1.5 mg	Zonnic® Cool mint 1.5 mg medicated chewing-gum

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC)

It was the responsibility of the investigator to obtain approval of the trial protocol/amendments from the Independent Ethics Committee (IEC) of the University of Lund, Sweden. The investigator filed all correspondence with the IEC. Copies of IEC approvals were to be forwarded to Niconovum AB.

A list of all IECs consulted is given in Appendix 16.1.3.

5.2 ETHICAL CONDUCT OF THE STUDY

This study was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions as well as International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

5.3 PATIENT INFORMATION AND CONSENT

It was the responsibility of the investigator to give each subject prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subjects were informed about their right to withdraw from the trial at any time. Written subject information was given to each subject before enrolment. Furthermore, it was the responsibility of the investigator to obtain signed informed consent from all subjects prior to inclusion in the trial.

Written information for the patient and a sample patient consent form is provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Role	Name, affiliation
Principal Investigator:	Elsy-Britt Schildt, MD Dept. of Oncology, University Hospital Lund SE-221 85 Lund, Sweden Phone: +46 46 177870 Mobile: + 46 709 203780 elsy-britt.schildt@med.lu.se
Co-Investigator:	Karl Olov Fagerström, PhD Smokers Information Centre Berga Allé 1 SE- 254 52 Helsingborg, Sweden Phone: +46 42 150650 Fax: +46 42 165760 Karl.fagerstrom@swipnet.se
Clinical Trial Coordinator:	Anders Axelsson, M.Sc. Pharm Niconovum AB Järnvägsg. 13 SE-252 24 Helsingborg, Sweden Phone: +46 42 199430 Fax: +46 42 199440 anders.axelsson@Niconovum.se
Study Monitor:	Helen Iwar, RN; BSc Trial Form Support AB S:t Lars v. 46 SE-222 70, Lund, Sweden Phone: +46 46 313200 helen.iwar@trialformsupport.com
Biostatistician:	Sven-Öjvind Swahn Cygnus data Tegnersgatan 19 SE-412 52 Gothenburg, Sweden Tel: + 46 (0)705 160924 Fax : +46 (0)31 160924

A list of investigators, including Curriculum Vitae and other persons whose participation materially affected the conduct of the study is included in Appendix 16.1.4.

7. INTRODUCTION

Zonnic® Cool mint 1.5 mg medicated chewing-gum is a Nicotine Replacement Therapy (NRT) developed at Niconovum AB.

The harmful effects of tobacco smoking upon health are well recognised within the medical community. Smoking cessation is therefore one of the most important measures to improve public health. It is also generally accepted that the difficulties in withdrawing from smoking result from the dependence on nicotine. One strategy to aid smoking cessation is to reduce withdrawal symptoms by providing nicotine in a different form, NRT. A number of NRT products have been developed and marketed to fulfil this need, e.g. chewing-gum, transdermal patches, nasal spray, "inhaler", sublingual and buccal tablets. The main mode of action of NRT is thought to be the stimulation of nicotinic receptors in specific target areas in the brain and the consequent release of dopamine. This leads to a reduction of nicotine withdrawal symptoms that contribute to nicotine addiction in regular smokers who try to abstain from smoking (1).

A Cochrane Review analysed the effectiveness of the different forms of NRT in achieving abstinence from cigarettes, or a sustained reduction in amount smoked. All commercially available forms of NRT (chewing-gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) were found to be effective as part of a strategy to promote smoking cessation. The available NRT formulations increase the odds of quitting approximately by 1.5- to 2-fold for smokers with moderate to severe nicotine dependence (2). The effectiveness of NRT appears to be largely independent of the intensity of other and additional forms of anti-smoking support provided. Importantly, even in subjects with established coronary disease, there is no evidence of negative health consequences resulting from use of the transdermal nicotine patch (2).

The rationale for the development of Zonnic® Cool mint 1.5 mg medicated chewing-gum ("Zonnic 1.5 mg") was to provide a choice of a coated chewing-gum bioequivalent to the registered Nicorette® 2 mg nicotine chewing gum Classic flavour ("Nicorette 2 mg"), which is assumed to yield approximately 1.4 mg nicotine. This was achieved by reducing the residual nicotine content in the Zonnic 1.5 mg chewing-gum after administration by using a physically and chemically stable nicotine carrier complex in a medicated chewing-gum produced by direct compression. Microcrystalline cellulose was chosen as carrier of nicotine because nicotine is more completely released from this carrier complex compared to the nicotine polacrilex complex, i.e. the residual nicotine content in the chewing-gum after administration is lower. Furthermore, Zonnic 1.5 mg is sugar-free, has a soft texture and does not contain buffering agents which might improve the taste of the product since sodium carbonate may have a soapy taste.

The clinical development programme of Zonnic® Cool mint 1.5 mg medicated chewing-gum comprises one previous randomised cross-over pharmacokinetic (PK) bioequivalence study, TS GU 03, comparing Zonnic 1.5 mg medicated chewing gum (two different flavours), Nicorette® 2 mg nicotine chewing gum Classic flavour and Nicorette® 4 mg nicotine chewing gum Classic flavour in healthy smokers.

Since smoking cessation programmes are considered to be some of the most cost-effective procedures in health care, continuous efforts have been made to improve their effectiveness over standard preparations. One such procedure is to alter the mode and rate of nicotine to the subject in order to mimic the concentrations of nicotine which takes place during smoking. In many countries, like Sweden, the chewing-gum formulation is the most preferred administration form. However, in order to reach effective concentrations of nicotine about 10-15 pieces/day needs to be chewed for 30 min each, i.e. 5-7.5 h of chewing/day. Zonnic® Cool mint 1.5 mg medicated chewing-gum is designed to be chewed for only 10 min. In this study chewing of Zonnic® Cool mint 1.5 mg medicated chewing-gum for 10 min and Nicorette® 2 mg nicotine chewing gum Classic flavour for 30 min were tested for bioequivalence.

8. STUDY OBJECTIVES

Primary Objective:
- To estimate the nicotine plasma concentrations following a single dose of Zonnic® Cool mint 1.5 mg medicated chewing-gum in comparison to Nicorette® 2 mg nicotine chewing gum Classic flavour when the Zonnic 1.5 mg product is chewed for 10 min and the Nicorette 2 mg product for 30 min.

Secondary Objectives:
- To assess craving for tobacco as a function of time since administration of study product and plasma concentration
- To estimate subjective time to effect and preference (Preference not recorded.)
- To compare the increases in nicotine plasma levels at 3, 6, 10 and 20 min resulting from the respective products.

Other Objectives:
- Relationship between dose and plasma concentrations of nicotine
- Population pharmacokinetics (PK).

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

The study was conducted as a randomised, open, two-period cross-over trial where the treatments, Zonnic® Cool mint 1.5 mg medicated chewing-gum and Nicorette® 2 mg nicotine chewing gum Classic flavour, were given to the subjects in random order at two different investigation days (treatment periods A, and B) separated by a wash-out period of at least 1 day.
All subjects were to receive both treatments. Single dose administrations were to be performed.
The products studied were:
Treatment A: Zonnic® Cool mint 1.5 mg medicated chewing-gum (“Zonnic 1.5 mg”)
Treatment B: Nicorette® 2 mg nicotine chewing gum Classic flavour (“Nicorette 2 mg”)

At the first visit eligibility to participate in the study was checked. The subject was given information about the study procedures and signed the informed consent form. At this visit the following procedures were conducted and documented:

- Informed consent
- Inclusion/Exclusion criteria
- Demographic data
- Body height and weight
- Supine blood pressure (BP) and heart rate (HR)
- Concurrent diseases/symptoms
- Concomitant medication

If the subject fulfilled all criteria for enrolment the subject was accepted for the study and started for the first administration of study drug. At the two visits confirmation of eligibility and measurement of exhaled carbon monoxide (ECO) were conducted and documented before administration of investigational drugs. Measurement of ECO was performed at each visit to confirm that the subject had abstained from smoking. Levels of ECO up to 10 ppm were considered compatible with abstinence. Concomitant medication was recorded. An intravenous (IV) cannula was administered for the blood sampling and blood was drawn at baseline (=0 min).

Administration of investigational drug occurred at time point 0 min. Zonnic 1.5 mg was chewed over 10 min while Nicorette 2 mg was chewed over 30 min using a metronome to standardise the chewing rate, one chew every two seconds.

Blood (5 ml) was drawn at baseline (=0 min) and then at 3, 6, 10, 20, 30, 45, 60 min and 1.5, 2, 3, 4, 5 and 6 h after drug administration for PK analysis of nicotine levels. Supine BP and HR were measured at the end of each study day. An adverse event (AE) interview (open questioning) was conducted at the end of each study day.

At time points 0, 3, 6, 10, 20 and 30 min, the subjects rated their craving on a visual analogue scale (VAS) on a line of 100 mm where one end was anchored as “no craving” and the other “extreme craving”. The subjects saw their previous ratings which is standard practice in studies of tobacco abstinence symptoms because it is easier for subjects to determine the degree of craving relative to past ratings and the variation thus decreases.

The nurses collecting blood samples were not allowed to handle any used or unused chewing-gum because of risk for contamination of the plasma. Frozen plasma samples collected for nicotine level determinations were shipped to a certified contract laboratory, ABS Laboratories, London, UK. Collection and shipping were handled according to standard operating procedures.

The bioequivalence between Zonnic® Cool mint 1.5 mg medicated chewing-gum and the Nicorette® 2 mg nicotine chewing gum Classic flavour was estimated by calculating the geometric mean and the 90% confidence interval (CI) for the quotients of maximum concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) from 0 to 6 h ($AUC_{0\text{-}6h}$) and from 0 hours to infinity (AUC_{inf}) corrected for baseline nicotine plasma

concentration ($_cAUC_{0-6h}$ and $_cAUC_{inf}$). Bioequivalence was to be declared if the quotients were contained within the limits 0.8–1.25. The differences between Zonnic 1.5 mg and Nicorette 2 mg are shown descriptively. Adverse events, tolerability self-reports and HR are reported descriptively.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The comparator was chosen based on the results of study TS GU 03 which showed bioequivalence between Zonnic 1.5 mg and Nicorette 2 mg. The rationale for the choice of study design was that Zonnic® Cool mint 1.5 mg medicated chewing-gum contains an amount of nicotine that was expected to be extracted to the same extent when chewed for 10 min as the Nicorette® 2 mg nicotine chewing gum Classic flavour when chewed for 30 min.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

- Consent to participate voluntarily and sign informed consent prior to any study procedure
- Healthy male and female, age 18 through 60 years
- Willing and able to chew nicotine chewing-gum
- Willing and able to comply with the study-specific procedures
- Smoker of >10 cigarettes/day.

9.3.2 Exclusion Criteria

Subjects fulfilling any of the following criteria were excluded from the study:

- Subjects who were participating in other drug studies or who had received other investigational drugs within 30 days prior to enrolment
- Subjects with any surgical or medical condition, which, in the judgement of the clinical investigator, might interfere with the absorption, distribution, metabolism or excretion of the drug
- Subjects who were using drugs capable of inducing hepatic enzyme metabolism (e.g., barbiturates, rifampin, carbamazepine, phenytoin, primidone) within the previous 30 days (or 5 half-lives of inducing agent, whichever was longer) of enrolment in this study
- Subjects with any of the following conditions:
  - Pregnancy
  - Severe cardiovascular disease
  - Vasospasm
  - Uncontrolled hypertonia
  - Moderate to severe liver disease
  - Severe kidney disease
  - Gastric or duodenal ulcer

- Feochromocytoma
- Hyperthyroidism.

9.3.3. Removal of Patients from Therapy or Assessment

A subject could be withdrawn from the trial treatment if, in the opinion of the investigator, it was medically necessary, or if it was the wish of the subject. In any circumstance, subject outcome was to be documented and a Study Termination Report completed.

9.4 TREATMENTS

9.4.1 Treatments Administered

Subjects were given single dose administrations of Zonnic® Cool mint 1.5 mg medicated chewing-gum and Nicorette® 2 mg nicotine chewing gum Classic flavour at two different occasions separated by at least one day. One piece of Zonnic 1.5 mg was chewed over 10 min while Nicorette 2 mg was chewed over 30 min using a metronome to standardise the chewing rate, one chew every two seconds.

9.4.2 Identity of Investigational Product(s)

Zonnic® Cool mint 1.5 mg medicated chewing-gum
Active ingredient: nicotine 1.61 mg
Excipients: gum base, maltitol, isomalt, mint flavours, talcum, magnesium stearate, microcrystalline cellulose, ascorbyl palmitate, acesulfame potassium, aspartame, acacia, titan dioxide and macrogol.

Batch No.: 08E50

Nicorette® 2 mg nicotine chewing-gum Classic flavour
Batch No.: KC179A

9.4.3 Method of Assigning Patients to Treatment Groups

The subjects were assigned a subject number in consecutive order as they entered the study. This number corresponded to a number on a computer-generated randomisation list, which decided the sequence of treatments. The subjects were randomised to one of two treatment sequences. The randomisation was performed using block randomisation. The randomisation list was produced by Cygnus Data.

Subjects replacing other subjects were to be given a new consecutive subject number, but were to undertake the investigational procedure in the sequence determined for the subject that he/she was replacing.

9.4.4 Selection of Doses in the Study

Selection of dose was based on the results of study TS GU 03 which showed bioequivalence between Zonnic 1.5 mg and Nicorette 2 mg.

9.4.5 Selection and Timing of Dose for Each Patient

Smoking was not allowed from 20.00 the night before treatment and not during treatment days. The subjects were instructed to eat breakfast before coming to the clinic. Acid drinks, coca-cola and coffee might decrease the absorption of nicotine through the mouth. The subjects were therefore not allowed to eat or drink during the nicotine gum chewing (first hour). A meal with drink was served at a specified time point on the treatment days.

9.4.6 Blinding

The study was open and randomised. Treatments were identical to the commercially available preparations (Zonnic® Cool mint 1.5 mg medicated chewing-gum and Nicorette® 2 mg nicotine chewing gum Classic flavour) and thus differed in appearance, application and use characteristics.

9.4.7 Prior and Concomitant Therapy

Over-the-counter (OTC) drugs were allowed up to 24 h before and after each dose of study medication. No prescription drugs or herbal remedies were allowed. Any such use in between study days was to be reported to the investigator. All concomitant medication was recorded in the appropriate section of the Case Report Form (CRF).

9.4.8 Treatment Compliance

Each dose was taken under supervision of the staff at the trial site.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Pharmacokinetic (PK) and Safety Measurements Assessed and Flow Chart

Demographics
All continuous variables are described using descriptive statistics, i.e. mean, standard deviation (SD), standard error of the mean, median, min, max, number of missing observations and number of observations. The categorical/dichotomies variables are described using frequency tables with number of observations and percentages. No formal hypothesis testing was carried out for these variables and all results are presented by treatment group.

Pharmacokinetic Measurements Assessed
Plasma samples drawn at regular intervals for up to 6 h after each dose administration were analysed for nicotine. Subjects who received one dose of both Zonnic 1.5 mg and Nicorette 2

mg were to be included in the PK analyses. Pharmacokinetic data were analysed using " PK functions for Microsoft Excel" by Usansky et al (3), at Allergan, Inc.
The C_{max} and the time to C_{max} (T_{max}) were determined from the observed plasma concentration-time curve. The AUC up to the last measurement, AUC_{0-6h} and AUC_{inf} are presented. Their values corrected for baseline nicotine (AUC_{0-6h} and $_cAUC_{inf}$) were used for the testing of bioequivalence. Maximum concentration, AUC_{0-6h} and $_cAUC_{inf}$ were tested for log-normality using the Shapiro-Wilks test.

The bioequivalence between Zonnic® Cool mint 1.5 mg medicated chewing-gum and Nicorette® 2 mg nicotine chewing gum Classic flavour was estimated by calculating the geometric mean and the 90% confidence interval (CI) for the quotients of $_cC_{max}$, $_cAUC_{0-6h}$ and $_cAUC_{inf}$. Bioequivalence was to be declared if the quotients were contained within the limits 0.8–1.25.
T_{max} is presented with median and range.

The period effects and carry-over effect were calculated using a cross-over analysis of variance (ANOVA) model.

Safety Measurements Assessed
Definition
An **AE** is any untoward medical occurrence in a patient or trial subject administered a drug or biologic (medicinal product) or using a medical device; the event does not necessarily have a causal relationship with that treatment or usage.
Adverse events include the following:
All suspected adverse reactions.
All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.

a. Apparently unrelated illnesses, including the worsening of a pre-existing illness (see Pre-existing Conditions, below).
b. Injury or accidents. Note that if a medical condition was known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as two separate AEs. The outcome of the accident (e.g., hip fracture secondary to the fall) should be recorded under Comments.
c. Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).
d. Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they were associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a patient with jaundice) should be described under Comments on the report of the clinical event rather than listed as a separate AE.

Pre-existing Conditions
In this trial, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pre-treatment medical history/physical examination form) were not to be reported as an AE unless the condition worsened or episodes increased in frequency during the AE reporting period.

Procedures
Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, were not to be reported as AEs. However, the medical condition for which the procedure was performed was to be reported if it met the definition of an AE. For example, an acute appendicitis beginning during the AE reporting period was to be reported as the AE and the resulting appendectomy noted under Comments.

Adverse Event Reporting Period
The AE-reporting period for this trial began upon receiving the first dose of the investigational drugs and ended at the final clinic visit.
In addition, any known untoward event that occurred subsequent to the AE-reporting period that the investigator assessed as possibly related to the investigational medication/product was also to be reported as an AE.

Seriousness (Gravity)
Each AE was to be classified by the investigator as serious or non-serious. This classification of the gravity of the event determined the reporting procedures to be followed.

An AE that met one or more of the following criteria/outcomes was to be classified as serious:
- Death
- Life-threatening (i.e., immediate risk of death)
- In-patient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect.

Other, Medical/Scientific Judgement
Medical judgement should be exercised in deciding whether a reaction was serious in other situations. Important adverse reactions that were not immediately life-threatening or did not result in death or hospitalisation but may jeopardise the patient should be considered serious.

Eliciting Adverse Event Information
The investigator was to report all directly observed AEs and all AEs spontaneously reported by the trial subject. The question asked was: “Have you noticed any changes in your health since we asked last?”

Reporting
If a serious AE (SAE) occurred, the Niconovum AB monitor was to be notified using the serious adverse event report (SAER) form (or within 24 h of awareness of the event by the investigator. The initial report was to be followed by submission of more detailed AE information on the SAER form within 5 working days of the event. If unexpected, SAEs were also to be reported immediately to the IEC and to the Swedish Medical Products Agency (MPA). Serious AEs were also to be reported on the clinical trial AE CRF.
The SAER form was not the same as the AE CRF, however, where the same data were collected, the forms had to be completed in a consistent manner. For example, the same AE term was to be used on both forms.

Non-serious AEs were to be reported on the AE CRFs, which were to be submitted to Niconovum AB as specified in the AE report submission procedure for this protocol.

Reporting requirements for AEs:

Gravity	Reporting Time	Type of Report
Serious	Within 24 h	Initial report on SAER
	Within 5 working days	Final report on SAER
Non-serious	Per CRF submission procedure	Appropriate CRFs

In the rare event that the investigator did not become aware of the occurrence of an SAE immediately (for example, if an outpatient trial subject initially sought treatment elsewhere), the investigator was to report the event within 24 h after learning of it and document his/her first awareness of the AE.

Recording Instructions
Adverse events were be recorded in the CRF as specified.
If required on the AE CRFs, the investigator was to use the adjectives mild, moderate, or severe to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades were defined as follows:

Mild: Does not interfere with subject's usual function
Moderate: Interferes to some extent with subject's usual function
Severe: Interferes significantly with subject's usual function

Note the distinction between the gravity and the intensity of an AE. **Severe** is a measure of intensity; thus, a severe reaction will not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.
The investigator should also be asked to assess the possible relationship between the AE and the investigational medication as well as any concomitant medications.

Follow-up of Adverse Events
All AEs were to be followed until they were resolved or the subject’s participation in the trial ends. Instructions for reporting changes in an ongoing AE during a subject's participation in the trial were provided in the instructions that accompanied the AE CRFs.
In addition, all serious AEs and those non-serious events assessed by the investigator as possibly related to the investigational medication/product should continue to be followed even after the subject's participation in the trial was over. Such events were to be followed until they resolved or until the investigator assessed them as “chronic” or “stable.” Resolution of such events was to be documented in the appropriate CRF.

A clinical interview for solicitation of AEs was performed after the treatment sessions.

Heart rate (HR) and blood pressure (BP) were measured before each administration of study product and at the end of the session (6 h).

Subjects who received at least one dose of the study drug are included in all safety analyses. Adverse events were classified using the WHO dictionary. Each AE was counted once according to the date of onset. If the onset was prior to the first dose of study drug and the event did not increase in severity after initiation of study drug, it was considered a pre-treatment event and should not be counted in the AE incidence tables. If the onset was prior to the first dose of study drug and the severity increased after baseline, the event was counted as an AE.
The incidence of SAEs is summarised by body system and preferred term; dosing phase; maximum severity; and relation to study drug. Data from subjects with SAEs and from patients who discontinued due to AEs are summarised and patient data listings are provided. Descriptive statistics are provided for AE results.
Changes in the physical examination from baseline to the 24 h follow-up are summarised.
Concomitant medications taken by patients are summarised by treatment period and drug class.

9.5.2 Appropriateness of Measurements

The determinations of nicotine were performed using capillary gas chromatography after a single liquid-liquid extraction of a basified plasma sample. A nitrogen selective detector provided high selectivity and sensitivity for the measurement of nicotine.
Standard measurements were used for safety.

9.5.3 Primary Efficacy Variable(s)

To compare the nicotine plasma concentrations following a single dose of Zonnic® Cool mint 1.5 mg medicated chewing-gum to those of Nicorette® 2 mg nicotine chewing gum Classic flavour. A statistical comparison of the AUC of Zonnic 1.5 mg to that of Nicorette 2 mg was made (=primary endpoint).

9.5.4 Drug Concentration Measurements

The determinations of nicotine were performed using capillary gas chromatography after a single liquid-liquid extraction of a basified plasma sample. A nitrogen selective detector provided high selectivity and sensitivity for the measurement of nicotine. The assays were performed at ABS Laboratories, London, England.

To quantify nicotine a multilevel calibration at seven concentrations was performed. The calibration line was fitted by means of a power curve fitting regression model. The samples were assayed once. If the sample showed concentrations considered by the Study Director to be outside those expected the sample was re-assayed. If the repeat assay gave a result differing more than ±10% of the first result a third analysis was performed, subject to the availability of sample. The limit of quantification was 0.5 ng/ml.

9.6 DATA QUALITY ASSURANCE

Monitoring visits at the trial site were made periodically during the trial, to ensure that all aspects of the protocol were followed. Source documents were reviewed for verification of agreement with data in the CRFs. The trial site could also be subject to quality assurance (QA) audit by an external auditor appointed by Niconovum AB. The investigator/institution guaranteed access to source documents by the monitor, the quality assurance auditor and appropriate regulatory agencies. It was important that the investigator and relevant personnel were available during the monitoring visits and possible audits and that sufficient time was devoted to the process.

A CRF was required and was to be completed for each included subject. The completed original CRFs are the sole property of Niconovum AB and should not be made available in any form to third parties, except for authorised representatives of appropriate Health/Regulatory Authorities, without written permission from Niconovum AB.

To enable evaluations and/or audits from Health Authorities/Niconovum AB, and to comply with international regulations, the investigator agreed to keep records, including the identity of all participating subjects, all original signed Informed Consent Forms, copies of all CRFs and detailed records of drug disposition for 15 years.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

The study design was a two-period cross-over. The wash-out periods are assumed to have eliminated all carry-over effects.

The main analyses on the primary PK variable were performed on both baseline-corrected and uncorrected values.

The main analyses were to be performed on the intention to treat (ITT) and per protocol (PP) population. The ITT population included subjects with PK measurements from at least one treatment period.

For PK-profiles, both individual curves and mean curves per treatment are presented. Continuous variables are summarised with n, mean, SD, median and range. Dichotomous and categorical variables are described with n and percent. 90% or 95% CIs are given where applicable.

All values for all variables are listed by subject and treatment in appendices.

Primary Efficacy Analysis
The primary efficacy analysis is the analysis of the PK variable AUC_{0-6h} based on baseline-corrected and uncorrected values in the ITT population of Zonnic 1.5 mg and Nicorette 2 mg. The AUC data are summarised per treatment period and for differences between treatments. Figures and tables with individual PK-profiles are given for all subjects in the ITT population for Zonnic 1.5 mg and Nicorette 2 mg.

Secondary Efficacy Analysis
The following PK variables are based on baseline-corrected values in the ITT population:

- C_{max} – Maximal plasma concentration
- T_{max} – Time to maximal plasma concentration
- $AUC_{(0-\infty)}$ – Area under curve from 0 h to infinity
- $AUC_{(0-24h)}$ – Area under curve from 0h to 24h (not performed since the half-life was approximately 1 hour)
- % extrapol ($AUC_{(0-\infty)}$ - $AUC_{(0-24h)}$ / $AUC_{(0-\infty)}$) (not performed since the half-life was approximately 1 hour)

The following PK variables are based on original raw values in ITT population:

- C_{max} – Maximal plasma concentration
- T_{max} – Time to maximal plasma concentration
- $AUC_{(0-\infty)}$ – Area under curve from 0 h to infinity

These secondary efficacy analyses were performed in exactly the same way as the primary efficacy analysis of PK. PK variables are summarised per treatment period and for differences between treatments. Figures with individual PK-profiles are given for all ITT subjects for both Zonnic 1.5 mg and Nicorette 2 mg.

Additional analyses not described in the statistical analysis plan were performed on log-transformed data (e-log uncorrected C_{max}, e-log baseline-corrected C_{max}, e-log uncorrected AUC_{inf} and e-log baseline-corrected AUC_{inf}) since the Guidance for Industry (Statistical Approaches to Establishing Bioequivalence Guidance) recommends that bioequivalence measures (e.g., AUC and C_{max}) be log-transformed using either common logarithms to the base 10 or natural logarithms (4).

Craving for tobacco as a function of time (0. 3, 6, 10, 20 and 30 min) since administration of study product was assessed by a VAS scale (0-100 mm). The data were transformed to loss of craving in order to obtain a positive area graphically by subtracting the VAS reading from 100. The craving is summarised per treatment period and for differences between treatments. The data are presented in tables by descriptive statistics, i.e. mean, SD, standard error of the mean, median, min, max, number of missing observations and number of observations as well as figures. The p-value for the difference between the two treatments at each time-point was calculated using the Wilcoxon Signed rank test. Moreover, AUC_{0-t} was determined for both treatments and the distributions of the inter-treatment changes are given descriptively as above together with 95% CI and the difference analysed with Wilcoxon Signed rank test.

Subjective time to effect (min) measured as when the subjects reported that they could feel an effect of the respective medications. The data are presented as Kaplan-Meier plots as this is the most appropriate method to analyse subsequently accumulating time effect data. In this case, the conventional time to survival is defined as time to effect. The difference between the two time-to-effect curves was assessed by Kaplan-Meier analysis with effect time, 95% CI and standard error.

Data on change in baseline-corrected plasma nicotine values between Zonnic 1.5 mg and Nicorette 2 mg at 3, 6, 10 and 20 min are summarised per treatment time period and for differences between the treatments. The data are presented in tables by descriptive statistics, i.e. mean, SD, standard error of the mean, median, min, max, number of missing observations and number of observations as well as figures. The p-value for the difference between two time-points was calculated using the Wilcoxon Signed rank test. Moreover, AUC_{0-t} was determined for both treatments and the distributions of the inter-treatment changes are given descriptively as above together with 95% CI and the difference analysed with Wilcoxon Signed rank test.

Safety Data
Subjects who received at least one dose of the study drug were included in all safety analyses.

Vital Signs
The vital signs values for the safety population are summarised at baseline and at the final visit together with change from baseline to final visit.

Adverse Events (AEs) and Withdrawals
Adverse events (AEs and SAEs) were to be coded and classified according to the Medical Dictionary for Regulatory Authorities (MedDRA). Each AE was to be counted once according to the date of onset. If the onset was prior to the first dose of study drug and the event did not increase in severity after initiation of study drug, it was to be considered a pre-treatment event and should not be counted in the AE incidence tables. If the onset was prior to the first dose of study drug and the severity increased after baseline, the event was to be counted as an AE.
The incidences of all treatment emergent AEs were tabulated by subject only and treatment.

Concomitant Medication
Concomitant medication was not coded. Concomitant medication is listed by treatment.

9.7.2 Determination of Sample Size

Linear PK has been shown for buccal administration of nicotine in the dose interval 1-4 mg. From published studies it is known that the mean ±SD AUC at steady state is about 13 ± 3 ng/ml x h for Nicorette® 2 mg nicotine chewing gum Classic flavour. Using the relative size of the released dose of the Zonnic 1.5 mg preparation, it was assumed that the mean AUC following administration of Zonnic 1.5 mg should also be about 13 ng/ml x h with a similar SD in the present study. Furthermore, it was assumed that a 15% difference of the means was acceptable in order to be well within the margins of bioequivalence (0.8-1.25). To assess the

bioequivalence between Zonnic 1.5 mg and Nicorette 2 mg it was estimated that 24 subjects were required.

Sample size was calculated using a formula from Lachin (5).

$$N = \frac{\sigma^2\left(Q_c^{-1} + Q_e^{-1}\right)\left(Z_\alpha + Z_\beta\right)^2}{\left(\upsilon_c - \upsilon_e\right)^2}$$

Where
σ^2 is the pooled variance between Zonnic 1.5 mg and Nicorette 2 mg
Q_c^{-1} is the proportion subjects in the Zonnic 1.5 mg group
Q_e^{-1} is the proportion subjects in the Nicorette 2 mg group
υ_c is the mean AUC in the Zonnic 1.5 mg group
υ_e is the mean AUC in the Nicorette 2 mg group
Z_α is the significance level
Z_β is the power of the study.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

There was no amendment to the study protocol.

Assessment of preference was a secondary objective according to the study protocol but was not included in the statistical analysis plan or the CRF and was not recorded.

Statistical analyses of bioequivalence data are typically based on a statistical model for the logarithm of the bioavailability measures (e.g., AUC and C_{max}). Additional analyses were performed on log-transformed data (e-log uncorrected C_{max}, e-log baseline-corrected C_{max}, e-log uncorrected AUC_{inf} and e-log baseline-corrected AUC_{inf}) since the Guidance for Industry (Statistical Approaches to Establishing Bioequivalence Guidance) recommends that bioequivalence measures (e.g., AUC and C_{max}) be log-transformed using either common logarithms to the base 10 or natural logarithms (4).

Elimination rate and half-life were not included in the statistical analysis plan but were calculated and are presented in the report.

In addition to the Wilcoxon Signed rank test specified in the study protocol, a two-tailed t-test was used for the PK results.

According to the statistical analysis plan, $AUC_{(0\text{-}24h)}$ and % extrapol ($AUC_{(0\text{-}\infty)}$ - $AUC_{(0\text{-}24h)}$ / $AUC_{(0\text{-}\infty)}$) were to be calculated but this was not meaningful since the half-life of nicotine in this single dose study was only approximately 1 hour.

According to the statistical analysis plan, AUC_{0-t} was to be calculated for craving but this was not meaningful with only four subjects who reached minimum craving during both Zonnic 1.5 mg and Nicorette 2 mg test periods.

Although not clearly stated in the study protocol, descriptive statistics of chewing-gum residual nicotine is reported.

10. STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

All enrolled 24 subjects completed both treatment periods.

10.2 PROTOCOL DEVIATIONS

All enrolled 24 subjects completed both treatment periods and all subject had a wash-out period of at least one day between the treatment periods (mean: 7.08 days; range: 2-14 days).

Thirty of the 672 samples were reported to have been taken later than scheduled in the protocol. Average for the 30 delayed samplings was 3 minutes 32 seconds, (SD: 2 minutes and 57 seconds). If sampling was delayed, correction was made using linear regression from the previous sample, please see Appendix 16.1.9 and Appendix 16.2.5.

Subject No. 23 was sterilized and did not perform a pregnancy test.

No other individual protocol deviations were reported and no subject had an ECO value above 10 ppm before study drug administration, Table 3 and Appendix 16.2.2.

11. PK AND EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

All enrolled 24 subjects completed both treatment periods and were included in both the PK and efficacy analyses. The ITT population was identical to the PP population.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The mean age of the subjects was 43 years (SD: 14 years). Mean weight was 83.5 kg (SD: 17.2 kg), mean height was 175 cm (SD: 9.4 cm) and mean BMI was 27.1 kg/m^2 (SD: 3.9 kg/m^2), Table 1. All 24 subjects were of Caucasian origin. Thirteen subjects (54%) were males and eleven were females (46%).

Table 1. Summary statistics of demographics

	N	Mean	SD	Min	Max	Median
Age at visit 0 (years)	24	43.3	13.6	18.3	60.7	47.0
Weight (kg)	24	83.5	17.2	62.0	117.0	77.2
Height (cm)	24	175	10	154	193.0	175.0
BMI (kg/m^2)	24	27.1	3.9	21.4	35.6	26.1

Ten (42%) of the subjects reported a medical history and eight (33%) of the subjects were on medication, Table 2.

Table 2. Medical history and concomitant medication

Subject No.	Description	Start date	Stop date if not ongoing	Concomitant medication	Dose/day	Indication	Start date:
5	Hypothyroidism	2005-02-01		Levaxin	50 µg	Hypothyroidism	2005-02-01
6	Asthma	1955		Omeprazol	20 mg	Dyspepsia	Unknown
				Stilnoct	10 mg	Insomnia	Unknown
7	Psoriasis	Unknown					
9	Insomnia	1996		Imovane	7.5 mg	Insomnia	Unknown
13	Cancer uteri	1993	1993				
15	Epilepsy	1979		Lamictal	400 mg	Epilepsy	May 2002
				Topamax	100 mg	Epilepsy	December 2005
18	Fibromyalgia	2001-01-01					
	Hysterectomy surgery	2003-01-01	2003				
19	Depression	2008-10-01		Citalopram	20 mg	Mood swings, depression	2008-10-01
23	Asthma	1955		Seretide	50 µg	Asthma	April 2002
	depression	2002-01-01		Femanest	2 mg	Hysterectomy	August 1993
24	Anxiety	2006-02-01		Cerazette	75 µg	Anti-conception	2004-02-01
				Efexor	150 mg	Anxiety/depression	2006-02-01

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Each dose was taken under supervision of the staff at the trial site. No subject had an ECO value above 10 ppm, Table 3.

Table 3. Exhaled carbon oxide (ECO) before administration of study drug

ECO before administration of study drug (ppm)	N	Mean	SD	Min	Max	Median
Zonnic 1.5 mg	24	6.00	2.81	1	10	6.5
Nicorette 2 mg	24	5.96	2.82	1	10	6.0

For listings of drug concentration data in plasma by subject, please see Appendix 16.2.5.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of PK and Efficacy

11.4.1.1 Analysis of PK

Normality Tests
Significance levels over 0.05 are consistent with the assumption of a normal distribution. The normality test of the difference between Zonnic 1.5 mg and Nicorette 2 mg in plasma nicotine levels (baseline-corrected data) showed that the data taken at T=20 minutes met the normality criterion while the others did not, Table 4.

Table 4. Normality test of the difference between Zonnic 1.5 mg and Nicorette 2 mg in plasma nicotine levels (baseline-corrected data)

Time point	Kolmogorov-Smirnov(a)			Shapiro-Wilk		
	Statistic	df	p-value	Statistic	df	p-value
3 min	0.262	24	0.000	0.751	24	0.000
6 min	0.200	24	0.014	0.891	24	0.014
10 min	0.194	24	0.020	0.910	24	0.036
20 min	0.099	24	0.200(*)	0.985	24	0.967

df: degrees of freedom
*A lower bound of the true significance.
[a]Lilliefors Significance Correction
[b]T_0_min is constant and has been omitted.

The normality test of the difference in change between Zonnic 1.5 mg and Nicorette 2 mg in plasma nicotine levels (baseline-corrected data) showed that samples taken at 3 and 10 minutes did not differ significantly, the others did, Table 5.

Table 5. Normality test of difference in change in baseline-corrected plasma nicotine levels between Zonnic 1.5 mg and Nicorette 2 mg and significance test of the difference

Time (min)	N	Mean	Median	Min	Max	Lower limit of 90% CI	Upper limit of 90% CI	Wilcoxon signed ranks test p-value
0	24	0	0	0	0			
3	24	0.07	0.04	-0.62	1.46	-0.12	0.26	0.742
6	24	0.58	0.34	-0.83	3.14	0.2	0.96	0.004
10	24	-0.07	0.32	-2.16	2.22	-0.53	0.39	0.797
20	24	-1.21	-0.95	-5.64	2.76	-2	-0.42	0.009

Table 6. Normality test of PK variables, Zonnic 1.5 mg and Nicorette 2 mg (uncorrected data)

		Kolmogorov-Smirnov(a)			Shapiro-Wilk		
		Statistic	df	p-value	Statistic	df	p-value
Zonnic 1.5 mg	C_{max}	0.330	24	0.000	0.518	24	0.000
	T_{max}	0.273	24	0.000	0.791	24	0.000
	AUC_{inf}	0.416	24	0.000	0.372	24	0.000
	LOGe_C_{max}	0.207	24	0.009	0.875	24	0.007
	LOGe_AUC_{inf}	0.250	24	0.000	0.696	24	0.000
Nicorette 2 mg	C_{max}	0.258	24	0.000	0.780	24	0.000
	T_{max}	0.332	24	0.000	0.484	24	0.000
	AUC_{inf}	0.297	24	0.000	0.550	24	0.000
	LOGe_C_{max}	0.172	24	0.064	0.940	24	0.159
	LOGe_AUC_{inf}	0.150	24	0.170	0.859	24	0.003

*This is a lower bound of the true significance.
[a]Lilliefors Significance Correction

Table 7. Normality test of PK variables, Zonnic 1.5 mg and Nicorette 2 mg (baseline-corrected data)

		Kolmogorov-Smirnov(a)			Shapiro-Wilk		
		Statistic	df	p-value	Statistic	df	p-value
Zonnic 1.5 mg	cC_{max}	0.124	24	0.200(*)	0.915	24	0.046
	T_{max}	0.273	24	0.000	0.791	24	0.000
	$cAUC_{inf}$	0.224	24	0.003	0.900	24	0.022
	$LOGe\_cC_{max}$	0.111	24	0.200(*)	0.955	24	0.354
	$LOGe\_cAUC_{inf}$	0.166	24	0.088	0.940	24	0.161
Nicorette 2 mg	cC_{max}	0.095	24	0.200(*)	0.978	24	0.852
	T_{max}	0.327	24	0.000	0.501	24	0.000
	$cAUC_{inf}$	0.116	24	0.200(*)	0.966	24	0.560
	$LOGe\_cC_{max}$	0.128	24	0.200(*)	0.961	24	0.454
	$LOGe\_cAUC_{inf}$	0.095	24	0.200(*)	0.962	24	0.481

*This is a lower bound of the true significance.
a Lilliefors Significance Correction

The difference in AUC_{0-6h} for Zonnic 1.5 mg minus Nicorette 2 mg did not pass the normality test, Table 8.

Table 8. Normality test of AUC_{0-6h}

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	p-value	Statistic	df	p-value
AUC_{0-6h}	0.219	24	0.004	0.909	24	0.034

*A lower bound of the true significance.
[a] Lilliefors Significance Correction

Non-transformed PK Data

The mean baseline-corrected maximum plasma nicotine concentration ($_cC_{max}$) was lower for Zonnic 1.5 mg (3.345 ng/ml; SD: 1.387 ng/ml) than for Nicorette 2 mg (5.154 ng/ml; SD: 1.628 ng/ml), Table 9 and Table 10. The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -1.810 ng/ml; 95% CI: -2.628 to -0.992) was statistically significant (two-tailed t-test: $p<0.001$; Wilcoxon Signed ranks test: $p=0.001$), Table 11. The mean quotient of $_cC_{max}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.701 with a 90% CI of 0.587 to 0.815, Table 12. Bioequivalence was not achieved as the quotient was not within the 0.8-1.25 limits.

The mean $AUC_{0\text{-}6h}$ corrected for baseline nicotine plasma concentration ($_cAUC_{0\text{-}6h}$) was lower for Zonnic 1.5 mg (6.910 ng x h/ml; SD: 2.458 ng x h/ml) than for Nicorette 2 mg (10.367 ng x h/ml; SD: 3.957 ng x h/ml), Table 9 and Table 10. The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -3.457 ng x h/ml; 95% CI: -5.402 to -1.512) was statistically significant (two-tailed t-test: $p=0.002$; Wilcoxon Signed ranks test: $p=0.001$), Table 11. The mean quotient of $_cAUC_{0\text{-}6h}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.782 with a 90% CI of 0.608 to 0.956, Table 12. Bioequivalence was not achieved as the quotient was not within the 0.8–1.25 limits.

The mean AUC_{inf} corrected for baseline nicotine plasma concentration ($_cAUC_{inf}$) was lower for Zonnic 1.5 mg (7.448 ng x h/ml; SD: 2.602 ng x h/ml) than for Nicorette 2 mg (10.993 ng x h/ml; SD: 4.159 ng x h/ml), Table 9 and Table 10. The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -3.544 ng x h/ml; 95% CI: -5.617 to -1.471) was statistically significant (two-tailed t-test: $p=0.003$; Wilcoxon Signed ranks test: $p=0.001$), Table 11. The mean quotient of $_cAUC_{inf}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.779 with a 90% CI of 0.634 to 0.924, Table 12. Bioequivalence was not achieved as the quotient was not within the 0.8–1.25 limits.

The mean T_{max} was similar for Zonnic 1.5 mg (0.729 h; SD: 0.462 h) and Nicorette 2 mg (0.694 h; SD: 0.522 h), Table 9 and Table 10. The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: 0.035 h; 95% CI: -0.237 to 0.307) was not statistically significant (two-tailed t-test: $p=0.804$; Wilcoxon Signed ranks test: $p=0.677$), Table 11.

The mean elimination rate was also similar for Zonnic 1.5 mg (0.661 h^{-1}; SD: 0.241 h^{-1}) and Nicorette 2 mg (0.700 h^{-1}; SD: 0.276 h^{-1}), Table 9 and Table 10. The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -0.039 h^{-1}; 95% CI: -0.167 to 0.089) was not statistically significant (two-tailed t-test: $p=0.557$; Wilcoxon Signed ranks test: $p=0.376$), Table 11.

The mean half-life was similar for Zonnic 1.5 mg (1.215 h; SD: 0.586 h) and Nicorette 2 mg (1.108 h; SD: 0.330 h), Table 9 and Table 10. The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: 0.107 h; 95% CI: -0.122 to 0.336) was not statistically significant (two-tailed t-test: $p=0.371$; Wilcoxon Signed ranks test: $p=0.391$), Table 11.

For tables on uncorrected values, please see Section 14.2.

Table 9. Summary statistics of PK variables for Zonnic 1.5 mg

	N	Mean	SD	Median	Min	Max	Lower limit of 95% CI	Upper limit of 95% CI
$_cC_{max}$ (ng/ml)	24	3.345	1.387	3.260	0.980	6.580	2.790	3.900
$_cAUC_{0\text{-}6h}$ (ng x h/ml)	24	6.910	2.458	6.131	2.821	12.553	5.927	7.893
$_cAUC_{inf}$ (ng x h/ml)	24	7.448	2.602	6.615	2.852	13.550	6.407	8.489
T_{max} (h)	24	0.729	0.462	0.500	0.333	2.000	0.544	0.914
Elimination rate (h^{-1})	24	0.661	0.241	0.650	0.196	1.291	0.565	0.757
Half-life (h)	24	1.215	0.586	1.067	0.537	3.533	0.981	1.449

Note: Baseline-subtracted values (negative values have been removed)

Table 10. Summary statistics of PK variables for Nicorette 2 mg

	N	Mean	SD	Median	Min	Max	Lower limit of 95% CI	Upper limit of 95% CI
$_cC_{max}$ (ng/ml)	24	5.154	1.628	5.090	2.610	8.430	4.503	5.805
$_cAUC_{0\text{-}6h}$ (ng x h/ml)	24	10.367	3.957	10.044	4.289	19.772	8.784	11.950
$_cAUC_{inf}$ (ng x h/ml)	24	10.993	4.159	10.428	5.587	21.631	9.329	12.657
T_{max} (h)	24	0.694	0.522	0.500	0.333	3.000	0.485	0.903
Elimination rate (h^{-1})	24	0.700	0.276	0.599	0.440	1.449	0.590	0.810
Half-life (h)	24	1.108	0.330	1.158	0.479	1.577	0.976	1.240

Note: Baseline-subtracted values (negative values have been removed)

Table 11. Summary statistics of PK variables for the difference Zonnic 1.5 mg minus Nicorette 2 mg

	N	Mean	SD	Median	Min	Max	Lower limit of 95% CI	Upper limit of 95% CI	t-test 2-tailed	Wilcoxon signed ranks test p-value
$_cC_{max}$ (ng/ml)	24	-1.810	2.045	-1.640	-6.020	2.330	-2.628	-0.992	0.000	0.001
$_cAUC_{0-6h}$ (ng x h/ml)	24	-3.457	4.861	-3.083	-14.612	8.265	-5.402	-1.512	0.002	0.001
$_cAUC_{inf}$ (ng x h/ml)	24	-3.544	5.182	-3.015	-15.903	7.963	-5.617	-1.471	0.003	0.001
T_{max} (h)	24	0.035	0.679	0.000	-2.250	1.250	-0.237	0.307	0.804	0.677
Elimination rate (h^{-1})	24	-0.039	0.320	-0.070	-0.948	0.844	-0.167	0.089	0.557	0.376
Half-life (h)	24	0.107	0.573	0.137	-1.016	2.093	-0.122	0.336	0.371	0.391

Note: Baseline-subtracted values (negative values have been removed)

Table 12. Summary statistics of PK variables for the quotients Zonnic 1.5 mg divided by Nicorette 2 mg

	N	Mean	SD	Median	Lower limit of 90% CI	Upper limit of 90% CI
$_cC_{max}$	24	0.701	0.341	0.704	0.587	0.815
$_cAUC_{0-6h}$	24	0.782	0.519	0.686	0.608	0.956
$_cAUC_{inf}$	24	0.779	0.433	0.714	0.634	0.924

Note: Baseline subtracted values (negative values have been removed)

Log-transformed PK Data

Based both on uncorrected data and baseline-corrected data, the difference in log-transformed values of C_{max} and AUC_{inf} between Zonnic 1.5 mg and Nicorette 2 mg was statistically significant, Table 13 and Table 14.

Table 13. Differences in PK values between Zonnic 1.5 mg and Nicorette 2 mg; Wilcoxon Signed Rank test (uncorrected data)

	N	Mean	SD	Median	Min	Max	Lower limit of 95% CI	Upper limit of 95% CI	t-test 2-tailed	Wilcoxon signed ranks test p-value
LOGe C_{max}	24	-0.357	0.332	-0.354	-0.901	0.298	-0.490	-0.224	0.000	0.000
LOGe AUC_{inf}	24	-0.176	0.308	-0.207	-0.815	0.591	-0.299	-0.053	0.010	0.010

Table 14. Differences in PK values between Zonnic 1.5 mg and Nicorette 2 mg; Wilcoxon Signed Rank test (baseline-corrected data)

	N	Mean	SD	Median	Min	Max	Lower limit of 95% CI	Upper limit of 95% CI	t-test 2-tailed	Wilcoxon signed ranks test p-value
LOGe cC_{max}	24	-0.464	0.478	-0.351	-1.389	0.437	-0.655	-0.273	0.000	0.001
LOGe $cAUC_{inf}$	24	-0.379	0.537	-0.339	-1.883	0.886	-0.594	-0.164	0.002	0.001

Bioequivalence

Statistical analyses of bioequivalence data are typically based on a statistical model for the logarithm of the bioavailability measures (e.g., AUC and C_{max}). Additional analyses were performed on log-transformed data since the Guidance for Industry (Statistical Approaches to Establishing Bioequivalence Guidance) recommends that bioequivalence measures (e.g., AUC and C_{max}) be log-transformed using either common logarithms to the base 10 or natural logarithms (4). Bioequivalence is considered to be present when the quotients of the AUC_{0-6h} and C_{max} of the logarithmically transformed data from the compared drugs are within the 0.8 - 1.25 range. A 90% CI is used for these calculations. Based on uncorrected data, AUC_{0-6h} (quotient: 0.913), C_{max} (quotient: 0.813) and AUC_{inf} (quotient: 0.946) all met the bioequivalence criteria. Based on baseline-corrected data, AUC_{0-6h} (quotient: 0.856) and AUC_{inf} (quotient: 0.861) but not C_{max} (quotient: 0.725) met the bioequivalence criteria, Table 15 and Table 16.

Table 15. Quotients of e-log PK data for Zonnic 1.5 mg divided by Nicorette 2 mg (uncorrected data)

	N	Mean	SD	Lower limit of 90% CI	Upper limit of 90% CI	Median
LOGe AUC_{0-6h}	24	0.913	0.078	0.887	0.939	0.920
LOGe C_{max}	24	0.813	0.175	0.754	0.872	0.832
LOGe AUC_{inf}	24	0.946	0.085	0.917	0.975	0.939

Table 16. Quotients of e-log PK data for Zonnic 1.5 mg divided by Nicorette 2 mg (baseline-corrected data)

	N	Mean	SD	Lower limit of 90% CI	Upper limit of 90% CI	Median
LOGe $cAUC_{0-6h}$	24	0.856	0.247	0.773	0.939	0.844
LOGe cC_{max}	24	0.725	0.310	0.621	0.829	0.751
LOGe $cAUC_{inf}$	24	0.861	0.213	0.789	0.933	0.855

11.4.1.2 Analysis of Efficacy

Subjective Time to Effect

The mean subjective time to effect measured on a VAS scale was shorter for Zonnic 1.5 mg (68.8 sec; SD: 35.8 sec) than for Nicorette 2 mg (135 sec; SD: 174 sec). The median subjective time to effect was 17.5 sec shorter with Zonnic 1.5 mg than with Nicorette 2 mg, Table 17.

Seventeen patients reported that the time to effect was shorter for Zonnic 1.5 mg than for Nicorette 2 mg while four patients reported that the time to effect was shorter for Nicorette 2 mg than for Zonnic 1.5 mg and three patients reported the time to effect to be equal for the two products, Table 18. Based on negative ranks, the time to effect for Nicorette 2 mg minus the time to effect for Zonnic 1.5 mg was -2.783 with a p-value of 0.005 in the two-tailed Wilcoxon Signed Ranks test (i.e., the time to effect was statistically significantly shorter for Zonnic 1.5 mg), Table 19.

The subjective time to effect is shown graphically in Figure 1. The two Kaplan-Meier functions are significantly different with the subjective time to effect being shorter for Zonnic 1.5 mg than for Nicorette 2 mg.

Table 17. Subjective time to effect: Zonnic 1.5 mg, Nicorette 2 mg and difference between Zonnic 1.5 mg and Nicorette 2 mg

Time to effect	N	Min (sec)	Max (sec)	Median (sec)	Mean			
					Mean (sec) Estimate	SD (sec)	95% CI	
							Lower limit (sec)	Upper limit (sec)
Zonnic 1.5 mg	24	30	150	50	68.8	35.8	54.4	83.1
Nicorette 2 mg	24	20	900	70	135.0	174.2	65.3	204.7
Zonnic 1.5 mg – Nicorette 2 mg	24	-800	45	-17.5	-66.3	165.9	-132.6	0.1

For the complete statistics please see Section 14.2.

Table 18. Subjective time to effect (ranks)

		N	Mean Rank	Sum of Ranks
Time to effect (Nicorette 2 mg) minus time to effect (Zonnic 1.5 mg)	Negative Ranks	4[a]	8.88	35.50
	Positive Ranks	17[b]	11.50	195.50
	Ties	3[c]		
	Total	24		

[a] Time to effect (Nicorette 2 mg) < Time to effect (Zonnic 1.5 mg)
[b] Time to effect (Nicorette 2 mg) > Time to effect (Zonnic 1.5 mg)
[c] Time to effect (Nicorette 2 mg) = Time to effect (Zonnic 1.5 mg)

Table 19. Significance test (Wilcoxon signed ranks test) of difference between Zonnic 1.5 mg and Nicorette 2 mg in subjective time to effect

	Time to effect (Zonnic 1.5 mg) minus time to effect (Nicorette 2 mg)
Zonnic 1.5 mg	-2.783 [a]
Asymptotic test (2-tailed)	0.005

[a] Based on negative ranks

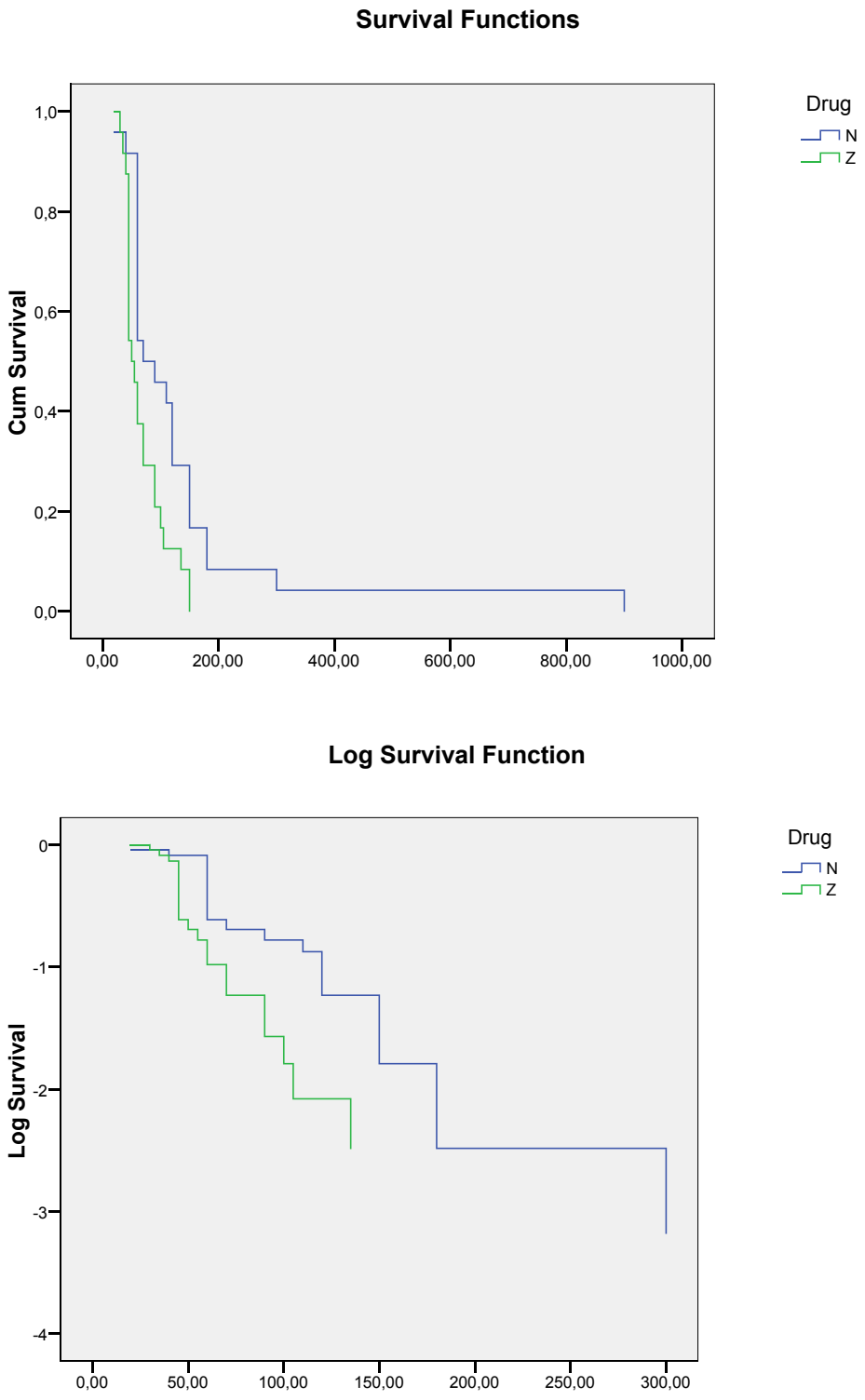


Figure 1. Kaplan Meier plots of time to effect

N= Nicorette 2 mg; Z=Zonnic 1.5 mg)

Craving
The highest mean craving score was observed at 5 minutes before administration of Zonnic 1.5 mg (57.9 mm; range: 8 mm-98 mm) or Nicorette 2 mg (59.5 mm; range: 5 mm-99 mm). Gradually lower mean craving scores were then reported with the lowest values at the last time point, 30 min, when the score was 21.5 mm (range: 1 mm-73 mm) with Zonnic 1.5 mg and 21.7 mm (range: 0 mm-82 mm) with Nicorette 2 mg, Table 20 and Table 21. Baseline-corrected values of tobacco craving are shown in Table 22 and Table 23, and are displayed graphically in Figure 2 and Figure 3.

Minimum craving during the 30-minute period was reported by 10 of 24 subjects (42%) receiving Zonnic 1.5 mg and 9 of 24 subjects receiving Nicorette 2 mg. Four subjects reached minimum craving during both Zonnic 1.5 mg and Nicorette 2 mg test periods.

There was no statistically significant difference in craving for tobacco between Zonnic 1.5 mg and Nicorette 2 mg at any given time point during the first 30 minutes of the study period. This pertained to both uncorrected and baseline-corrected data, Table 24.

Table 20. Zonnic 1.5 mg: Craving for tobacco (uncorrected data)

Time point (minutes)	Mean (mm)	SD (mm)	Min (mm)	Max (mm)	Median (mm)	N
-5	57.9	25.8	8	98	57	24
0	55.2	29.0	3	98	52	24
2.5	37.5	32.6	0	96	32	24
5	32.3	32.1	0	95	26	24
10	26.0	26.7	0	94	21	24
15	24.0	23.8	0	86	22	24
20	21.8	22.0	1	79	22	24
30	21.5	21.0	1	73	18	24

Table 21. Nicorette 2 mg: Craving for tobacco (uncorrected data)

Time point (minutes)	Mean (mm)	SD (mm)	Min (mm)	Max (mm)	Median (mm)	N
-5	59.5	29.6	5	99	62	24
0	54.5	28.3	5	98	54	24
2.5	41.7	29.7	1	96	39	24
5	34.2	27.3	2	97	30	24
10	28.0	27.4	1	97	24	24
15	24.5	27.4	0	94	18	24
20	22.2	25.6	0	91	15	24
30	21.7	24.9	0	82	13	24

Table 22. Zonnic 1.5 mg: Craving for tobacco (baseline-corrected data)

Time point (minutes)	Mean (mm)	SD (mm)	Min (mm)	Max (mm)	Median (mm)	N
-5	1.31	4.28	-4.36	15.13	7.18	24
0	-1.31	4.28	-15.13	4.36	-7.18	24
3	-19.07	16.95	-54.21	-0.62	-19.49	24
5	-24.26	16.64	-53.59	-2.15	-22.82	24
10	-30.58	16.95	-56.67	-3.18	-32.56	24
15	-32.53	17.57	-62.82	-4.67	-39.91	24
20	-34.77	18.96	-74.10	-5.38	-41.54	24
30	-35.06	20.11	-79.74	-3.54	-34.10	24

Table 23. Nicorette 2 mg: Craving for tobacco (baseline-corrected data)

Time point (minutes)	Mean (mm)	SD (mm)	Min (mm)	Max (mm)	Median (mm)	N
-5	2.46	7.90	-3.08	34.62	0.26	24
0	-2.46	7.90	-34.62	3.08	-0.26	24
3	-15.35	18.27	-62.31	1.23	-8.21	24
5	-22.76	17.88	-61.28	-0.26	-19.23	24
10	-29.04	20.19	-62.51	-0.26	-25.13	24
15	-32.47	21.75	-71.79	-3.33	-29.23	24
20	-34.84	22.10	-72.31	-3.59	-31.97	24
30	-35.29	23.63	-72.82	6.15	-28.97	24

Figure 2. Tobacco craving vs. time; medians of baseline-corrected values for Zonnic 1.5 mg and Nicorette 2 mg

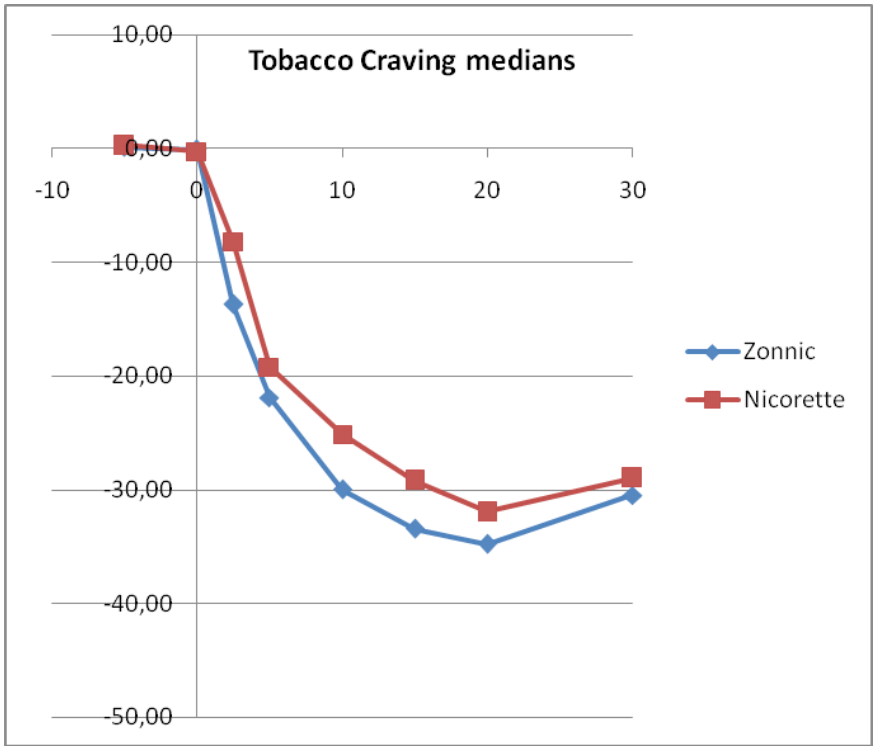


Figure 3. Tobacco craving vs. time; means and 95% CI of baseline-corrected values for Zonnic 1.5 mg and Nicorette 2 mg

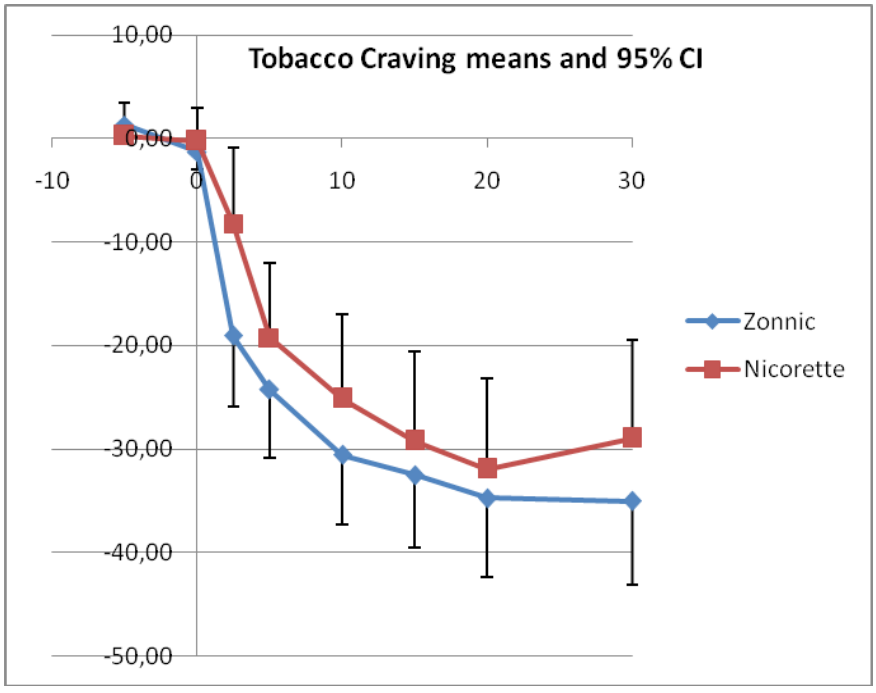


Table 24. Significance test (Wilcoxon Signed Ranks Test) of difference in craving between Nicorette 2 mg and Zonnic 1.5 mg, by time point

		Pre-dose	0 min	3 min	5 min	10 min	15 min	20 min	30 min
Difference Nicorette minus Zonnic	Uncorrected data	-0.400[a]	-0.122[b]	-1.110[a]	-0.800[a]	-1.272[a]	-0.882[a]	-0.701[a]	-0.390[a]
Asymptotic test (2-tailed)		0.689	0.903	0.267	0.424	0.204	0.378	0.483	0.697
Difference Nicorette minus Zonnic	Baseline-corrected data	-0.700[a]	-0.700[b]	-0.629[a]	-0.029[a]	-0.286[a]	-0.143[a]	-0.057[a]	-0.414[b]
Asymptotic test (2-tailed)		0.484	0.484	0.530	0.977	0.775	0.886	0.954	0.679

[a] Based on negative ranks.
[b] Based on positive ranks.

Chewing-gum Residual Nicotine

The mean chewing-gum residual nicotine amount was lower for Zonnic 1.5 mg (0.0877 mg; SD: 0.0246 mg) than for Nicorette 2 mg (0.1896 mg; SD: 0.8637 mg), Table 25. Two outliers were identified, please see Appendix 16.1.9.

Table 25. Chewing-gum nicotine residues

		Mean	SD	Median	Min	Max	Lower limit of 95% CI	Upper limit of 95% CI
Zonnic 1.5 mg	Nicotine (mg)	0.0877	0.0246	0.0856	0.0335	0.1358	0.0779	0.0976
	Weight (g)	0.5531	0.0775	0.5478	0.3954	0.7282	0.5221	0.5841
Nicorette 2 mg	Nicotine (mg)	0.1896	0.2516	0.1191	0.0544	1.0230	0.0889	0.2902
	Weight (g)	0.8637	0.0148	0.8627	0.8318	0.8961	0.8578	0.8696

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

No adjustments were performed for covariates such as gender, age, tobacco consumption pattern or anthropometric variables.

11.4.2.2 Handling of Dropouts or Missing Data

No adjustments for data loss (missing data) were performed since all subjects underwent the full study protocol.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed.

11.4.2.4 Multicentre Studies

Not applicable since this was a single centre study.

11.4.2.5 Multiple Comparison/Multiplicity

No adjustments were made for multiple comparisons.

11.4.2.6 Use of an "Efficacy Subset" of Patients

Not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Bioequivalence was calculated on both baseline-corrected data and the natural logarithm of PK data.

11.4.2.8 Examination of Subgroups

Not applicable.

11.4.3 Tabulation of Individual Response

Please see listings by subject in Appendix 16.2 for individual response data.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Correlation between tobacco craving and nicotine levels

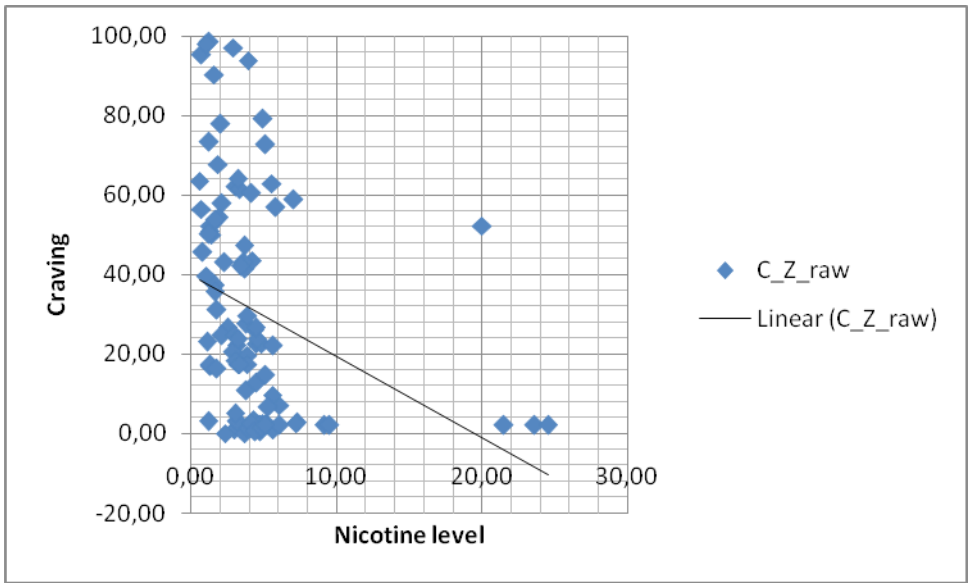
There was a statistically significant negative correlation between tobacco craving and plasma nicotine level, Table 26 and Table 27. This pertained to both uncorrected and baseline-corrected data.

Table 26. Zonnic 1.5 mg: correlation between tobacco craving and nicotine level (uncorrected data)

		Nicotine Zonnic 1.5 mg	Craving Zonnic 1.5 mg
Nicotine Zonnic 1.5 mg	Pearson Correlation	1	-0.307(**)
	Sig. (2-tailed)		0.002
	N	96	96

**Correlation is significant at the 0.01 level (2-tailed).

Figure 4. Zonnic 1.5 mg: tobacco craving vs. nicotine level (uncorrected data)



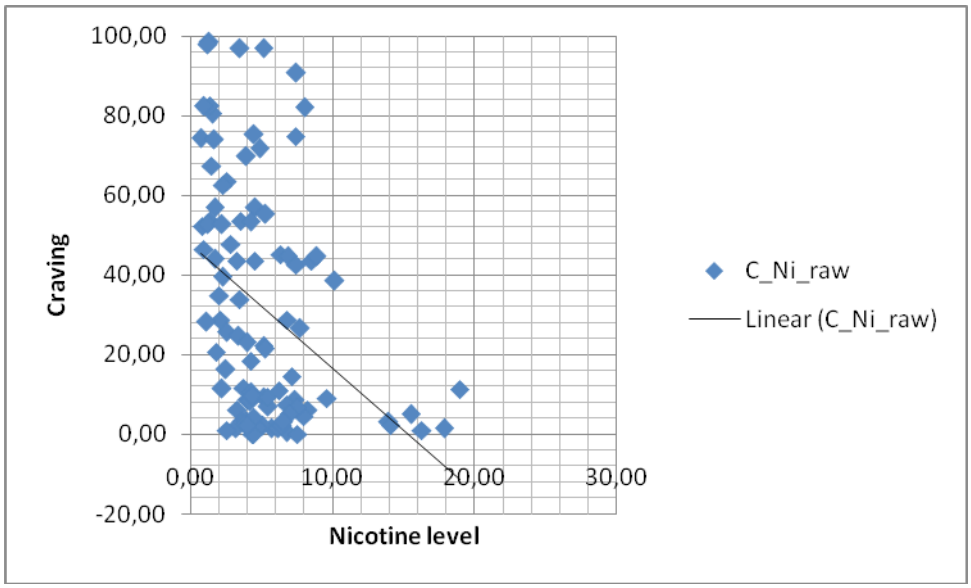
C=Tobacco craving in mm; Z=Zonnic 1.5 mg

Table 27. Nicorette 2 mg: correlation between tobacco craving and nicotine level (uncorrected data)

		Nicotine Nicorette 2 mg	Craving Nicorette 2 mg
Nicotine Nicorette 2 mg	Pearson Correlation	1	-0.386(**)
	Sig. (2-tailed)		0.000
	N	96	96

**Correlation is significant at the 0.01 level (2-tailed).

Figure 5. Nicorette 2 mg: tobacco craving vs. nicotine level, (uncorrected data)



C=Tobacco craving in mm; N= Nicorette 2 mg

11.4.5 Drug-Drug and Drug-Disease Interactions

Drug-drug or drug-disease interactions were not studied.

11.4.6 By-Patient Displays

Please see listings by subject in Appendix 16.2 for individual response data.

11.4.7 PK and Efficacy Conclusions

The mean $_{c}C_{max}$ was lower for Zonnic 1.5 mg (3.35 ng/ml; SD: 1.39 ng/ml) than for Nicorette 2 mg (5.15 ng/ml; SD: 1.63 ng/ml). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -1.81 ng/ml; 95% CI: -2.63 to -0.99) was statistically significant (two-tailed t-test: $p<0.001$; Wilcoxon Signed ranks test: $p=0.001$). The mean quotient of $_{c}C_{max}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.70 with a 90% CI of 0.59 to 0.82.

The mean $_{c}AUC_{0\text{-}6h}$ was lower for Zonnic 1.5 mg (6.91 ng x h/ml; SD: 2.46 ng x h/ml) than for Nicorette 2 mg (10.37 ng x h/ml; SD: 3.96 ng x h/ml). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -3.46 ng x h/ml; 95% CI: -5.40 to -1.51) was statistically significant (two-tailed t-test: $p=0.002$; Wilcoxon Signed ranks test: $p=0.001$). The mean quotient of $_{c}AUC_{0\text{-}6h}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.78 with a 90% CI of 0.61 to 0.96.

Also the mean $_{c}AUC_{inf}$ was lower for Zonnic 1.5 mg (7.45 ng x h/ml; SD: 2.60 ng x h/ml) than for Nicorette 2 mg (10.99 ng x h/ml; SD: 4.16 ng x h/ml). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: -3.54 ng x h/ml; 95% CI: -5.62 to -1.47) was statistically

significant (two-tailed t-test: p=0.003; Wilcoxon Signed ranks test: p=0.001). The mean quotient of ${}_cAUC_{inf}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.78 with a 90% CI of 0.63 to 0.92.

Based on non-transformed PK data, bioequivalence was not achieved as the quotients for ${}_cC_{max}$, ${}_cAUC_{0-6h}$ and ${}_cAUC_{inf}$ were not within the 0.8-1.25 limits. Because bioequivalence is generally considered to be present when the quotients of the AUC_{0-t} and C_{max} of the logarithmically transformed data from the compared drugs are within the 0.8 - 1.25 range, additional analyses using logarithmically transformed data were performed. Based on uncorrected log-transformed data, AUC_{0-6h} (quotient: 0.91), C_{max} (quotient: 0.81) and AUC_{inf} (quotient: 0.95) all met the bioequivalence criteria. Based on baseline-corrected log-transformed data, AUC_{0-6h} (quotient: 0.86) and AUC_{inf} (quotient: 0.86) but not C_{max} (quotient: 0.73) met the bioequivalence criteria.

The mean T_{max} was similar for Zonnic 1.5 mg (0.73 h, i.e. 44 min) and Nicorette 2 mg (0.69 h, i.e. 42 min). The difference of Zonnic 1.5 mg minus Nicorette 2 mg (mean: 0.035 h, i.e. 2 min) was not statistically significant (two-tailed t-test: p=0.80; Wilcoxon Signed ranks test: p=0.677).

The mean subjective time to effect measured on a VAS scale was shorter for Zonnic 1.5 mg (68.8 sec; SD: 35.8 sec) than for Nicorette 2 mg (135 sec; SD: 174 sec). The median subjective time to effect was 17.5 sec shorter with Zonnic 1.5 mg than with Nicorette 2 mg. Based on negative ranks, the time to effect was statistically significantly shorter for Zonnic 1.5 mg with a p-value of 0.005 in the two-tailed Wilcoxon Signed Ranks test.

The highest mean craving score was observed at 5 minutes before administration of Zonnic 1.5 mg (57.9 mm; range: 8 mm-98 mm) or Nicorette 2 mg (59.5 mm; range: 5 mm-99 mm). Gradually lower mean craving scores were then reported with the lowest values at the last time point, 30 min, when the score was 21.5 mm (range: 1-73 mm) during the Zonnic 1.5 mg period and 21.7 mm (range: 0 mm-82 mm) during the Nicorette 2 mg period. Minimum craving during the 30-minute period was reported by 10 of 24 subjects (42%) receiving Zonnic 1.5 mg and 9 of 24 subjects receiving Nicorette 2 mg. There was no statistically significant difference in craving tobacco between Zonnic 1.5 mg and Nicorette 2 mg at any given time point during the first 30 minutes of the study period. There was a statistically significant negative correlation between tobacco craving and plasma nicotine level, i.e. craving decreased with increasing nicotine levels.

The mean residual nicotine amount in the chewing-gum after chewing was lower for Zonnic 1.5 mg (0.088 mg; SD: 0.025 mg) than for Nicorette 2 mg (0.19 mg; SD: 0.86 mg).

12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

All 24 subjects received a single administration of Zonnic® Cool mint 1.5 mg medicated chewing-gum chewed for 10 min and a single administration of Nicorette® 2 mg nicotine chewing gum Classic flavour chewed for 30 min.

12.2 ADVERSE EVENTS (AEs)

No adverse events were reported during the study.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths, serious adverse events or other significant events occurred during the study.

12.4 CLINICAL LABORATORY EVALUATION

Not applicable since no clinical laboratory evaluation was performed.

12.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

The mean heart rate (HR) was similar before (74.4 bpm) and after (73.0 bpm) administration of Zonnic 1.5 mg. The mean HR was similar also before (73.7 bpm) and after (72.3 bpm) administration of Nicorette 2 mg, Table 28 and Table 29.

Furthermore, the mean blood pressure (BP) was similar before and after administration of Zonnic 1.5 mg (before: 119/71 mm Hg; after: 117/70 mm Hg) and Nicorette 2 mg (before: 119/71 mm Hg; after: 114/70 mm Hg), Table 28 and Table 29.

There were no statistically significant differences in change in HR or BP between Zonnic 1.5 mg and Nicorette 2 mg, Table 30.

Table 28. Heart rate and blood pressure before and after administration of Zonnic 1.5 mg

Zonnic 1.5 mg	N	Mean	SD	Lower limit of 95% CI	Upper limit of 95% CI	Median	Min	Max
Heart rate before (bpm)	24	74.42	9.40	70.66	78.18	77.00	56	94
Heart rate after (bpm)	24	73.04	9.17	69.37	76.71	76.00	60	86
Systolic BP before (mm Hg)	24	119.29	14.89	113.34	125.25	120.00	95	160
Systolic BP after (mm Hg)	24	117.00	14.09	111.36	122.64	117.50	95	155
Diastolic BP before (mm Hg)	24	71.46	8.14	68.20	74.71	72.50	60	85
Diastolic BP after (mm Hg)	24	70.21	8.53	66.80	73.62	70.00	60	85

Table 29. Heart rate and blood pressure before and after administration of Nicorette 2 mg

Nicorette 2 mg	N	Mean	SD	Lower limit of 95% CI	Upper limit of 95% CI	Median	Min	Max
Heart rate before (bpm)	24	73.71	11.02	69.30	78.12	78.00	50	96
Heart rate after (bpm)	24	72.29	8.84	68.75	75.83	73.50	54	88
Systolic BP before (mm Hg)	24	119.17	14.19	114.49	125.85	120.00	90	150
Systolic BP after (mm Hg)	24	114.17	10.49	109.97	118.37	110.00	95	135
Diastolic BP before (mm Hg)	24	70.83	10.90	66.47	75.19	70.00	50	90
Diastolic BP after (mm Hg)	24	70.00	7.80	66.88	73.12	70.00	60	85

Table 30. Non-parametric test of difference in heart rate and blood pressure

	Diff HR after -before Nicorette 2 mg minus diff HR after –before Zonnic 1.5 mg	Diff SBP after -before Nicorette 2 mg minus diff SBP after -before Zonnic 1.5 mg	Diff DBP after -before Nicorette 2 mg minus diff DBP after -before Zonnic 1.5 mg
Zonnic 1.5 mg	-0.456[a]	-0.868[b]	-0.087[a]
Asymptotic significance test (2-tailed)	0.649	0.385	0.930

[a]Based on positive ranks; [b]Based on negative ranks; [c]Wilcoxon Signed Ranks Test

12.6 SAFETY CONCLUSIONS

All enrolled 24 subjects completed both treatment periods. No adverse events were reported in this study and no safety concerns were identified.

13. DISCUSSION AND OVERALL CONCLUSIONS

In this study including 24 healthy smokers, the mean baseline-corrected maximum plasma nicotine concentration ($_cC_{max}$) was lower for Zonnic® Cool mint 1.5 mg medicated chewing-gum (3.3 ng/ml) chewed for 10 min than for Nicorette® 2 mg nicotine chewing gum Classic flavour (5.2 ng/ml) chewed for 30 min. The mean quotient of $_cC_{max}$ (Zonnic 1.5 mg divided by Nicorette 2 mg) was 0.70 with a 90% CI of 0.59 to 0.82. Also the mean $_cAUC_{0-6h}$ and $_cAUC_{inf}$ were lower for Zonnic 1.5 mg than for Nicorette 2 mg, both with a mean quotient (Zonnic 1.5 mg divided by Nicorette 2 mg) of 0.78. Bioequivalence is considered to be present when the quotients of the AUC_{0-t} and C_{max} of the logarithmically transformed data from the compared drugs (4) are within the 0.8 - 1.25 range. A 90% CI is used for these calculations. Based on uncorrected log-transformed data, AUC_{0-6h} (quotient: 0.913), C_{max} (quotient: 0.813) and AUC_{inf} (quotient: 0.946) all met the bioequivalence criteria. Based on baseline-corrected log-transformed data, AUC_{0-6h} (quotient: 0.86) and AUC_{inf} (quotient: 0.86) but not C_{max} (quotient: 0.73) met the bioequivalence criteria.

These results are in contrast to the results of study TS GU 03 which showed higher quotients for AUC and C_{max} (Zonnic divided by Nicorette). However, Nicorette 2 mg surprisingly yielded 1.8 mg nicotine in this study compared to 1.4 mg as stated by the Swedish MPA.

The mean T_{max} was similar for Zonnic® Cool mint 1.5 mg medicated chewing-gum (44 min) and Nicorette® 2 mg nicotine chewing gum Classic flavour (42 min). Also the mean elimination rate and the mean half-life were similar for Zonnic 1.5 mg and Nicorette 2 mg.

The mean subjective time to effect measured on a VAS scale was statistically significantly shorter for Zonnic 1.5 mg (68.8 sec) than for Nicorette 2 mg (135 sec) with a p-value of 0.005 in the two-tailed Wilcoxon Signed Ranks test. The fast onset of action allows a rapid relief of craving symptoms.

The highest mean craving score was observed at 5 minutes before administration of Zonnic 1.5 mg or Nicorette 2 mg. Gradually lower mean craving scores were then reported for both products with the lowest values at the last time point, 30 min. There was no statistically significant difference in craving for tobacco between Zonnic 1.5 mg and Nicorette 2 mg at any given time point during the first 30 minutes of the study period. As expected, there was a statistically significant negative correlation between tobacco craving and plasma nicotine level, i.e. craving decreased with increasing nicotine levels.

It was confirmed that the mean residual nicotine content after chewing was lower for Zonnic 1.5 mg (approx. 0.09 mg) than for Nicorette 2 mg (approx. 0.19 mg).

No adverse events were reported in this study and no safety concerns were identified.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

All tables on demographic data are presented in Section 11.2 or Appendix 16.2.1.

14.2 EFFICACY DATA

Table 14.2.1 Summary statistics of PK uncorrected data for Zonnic 1.5 mg (before baseline correction and removal of negative values)

Time (h)	Mean	SD	Median	Q1	Q3	Min	Max	Range	Lower limit of 95% CI	Upper limit of 95% CI
0.000	2.420	3.910	1.360	1.190	1.938	0.610	20.030	19.420	0.856	3.984
0.050	2.507	3.856	1.570	1.258	2.125	0.510	19.860	19.350	0.964	4.050
0.100	3.535	3.920	2.535	1.943	3.495	0.840	20.790	19.950	1.967	5.103
0.170	4.389	3.894	3.575	2.995	4.393	1.070	21.520	20.450	2.831	5.947
0.330	5.235	4.229	4.525	3.520	5.043	1.650	23.630	21.980	3.543	6.927
0.500	5.325	4.402	4.440	3.625	5.170	1.670	24.530	22.860	3.564	7.086
0.750	5.118	4.645	4.125	3.570	4.833	1.560	25.840	24.280	3.260	6.976
1.000	4.923	4.812	3.860	3.318	4.728	1.650	26.610	24.960	2.998	6.848
1.500	4.521	4.694	3.400	2.883	4.093	1.640	25.750	24.110	2.643	6.399
2.000	4.059	4.466	2.770	2.460	3.598	1.700	24.080	22.380	2.272	5.846
3.000	3.399	4.001	2.265	1.895	3.040	1.590	21.010	19.420	1.798	5.000
4.000	2.779	3.702	1.740	1.490	2.155	1.140	19.380	18.240	1.298	4.260
5.000	2.382	3.330	1.465	1.258	1.770	0.890	17.320	16.430	1.050	3.714
6.000	2.160	3.146	1.360	1.080	1.633	0.790	16.320	15.530	0.901	3.419

Table 14.2.2 Summary statistics of PK uncorrected (raw) data for Nicorette 2 mg (before baseline correction and removal of negative values)

Time (h)	Mean	SD	Median	Q1	Q3	Min	Max	Range	Lower limit of 95% CI	Upper limit of 95% CI
0.000	2.443	3.005	1.660	1.258	2.320	0.710	15.500	14.790	1.241	3.645
0.050	2.457	2.995	1.540	1.280	2.233	0.730	15.260	14.530	1.259	3.655
0.100	2.978	2.895	2.315	1.635	2.983	0.880	15.380	14.500	1.820	4.136
0.170	4.482	3.006	3.920	3.273	4.523	1.160	16.280	15.120	3.279	5.685
0.330	6.468	3.350	5.545	4.423	7.360	2.800	17.860	15.060	5.128	7.808
0.500	7.280	3.380	6.860	5.263	7.990	3.240	18.940	15.700	5.928	8.632
0.750	6.868	3.378	6.225	5.050	7.160	3.490	19.750	16.260	5.517	8.219
1.000	6.125	3.218	5.565	4.523	6.235	2.760	18.700	15.940	4.838	7.412
1.500	5.134	3.083	4.315	3.705	4.965	2.560	17.150	14.590	3.901	6.367
2.000	4.583	2.842	3.665	3.163	4.978	2.410	14.900	12.490	3.446	5.720
3.000	3.940	2.523	2.980	2.435	4.275	1.800	13.050	11.250	2.931	4.949
4.000	3.163	2.372	2.155	1.813	3.425	1.270	12.160	10.890	2.214	4.112
5.000	2.590	1.957	1.950	1.693	2.635	1.100	10.320	9.220	1.807	3.373
6.000	2.190	1.853	1.600	1.440	2.355	0.870	10.000	9.130	1.449	2.931

Table 14.2.3 PK uncorrected (raw) data for Zonnic 1.5 mg divided by Nicorette 2 mg (before baseline correction and removal of negative values)

	Mean	SD	Lower limit of 90% CI	Upper limit of 90% CI	Median	Q1	Q3
C_{max}	0.737	0.245	0.655	0.819	0.702	0.548	0.897
AUC_360	0.796	0.218	0.723	0.869	0.779	0.689	0.881
AUC_inf	0.879	0.294	0.780	0.978	0.814	0.727	1.021

Table 14.2.4 Descriptive statistics, time to effect

	N	Range	Min	Max	Mean		SD	Variance
					Estimate	Std error		
Time to effect – Zonnic 1.5 mg	24	120	30	150	68.75	7.306	35.791	1280.978
Time to effect – Nicorette 2 mg	24	880	20	900	135.00	35.550	174.156	30330.435
Valid N (listwise)	24							

Table 14.2.5 Means and medians for survival time (time to effect)

Drug	Mean(a)				Median			
	Estimate	Std. Error	95% CI		Estimate	Std. Error	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Nicorette 2 mg	135.000	35.550	65.323	204.677	70.000	14.289	41.994	98.006
Zonnic 1.5 mg	68.750	7.306	54.431	83.069	50.000	4.082	41.998	58.002
Overall	101.875	18.591	65.437	138.313	60.000	3.699	52.751	67.249

[a] Estimation is limited to the largest survival time if it is censored.

Table 14.2.6 Descriptive statistics, time to effect

Time to effect	N	Mean	SD	Min	Max	Percentiles		
						75th	25th	50th (Median)
Zonnic 1.5 mg	24	68.75	35.79076	30	150	45.00	52.50	90.00
Nicorette 2 mg	24	135.00	174.15635	20	900	60.00	80.00	150.00

Table 14.2.7 Survival table, time to effect

Drug		Time	Status	Cumulative proportion surviving at the time		No. of cumulative events	No. of remaining cases
		Estimate	Std. Error	Estimate	Std. Error	Estimate	Std. Error
Nicorette 2 mg	1	20	1	0.958	0.041	1	23
	2	40	1	0.917	0.056	2	22
	3	60	1	.	.	3	21
	4	60	1	.	.	4	20
	5	60	1	.	.	5	19
	6	60	1	.	.	6	18
	7	60	1	.	.	7	17
	8	60	1	.	.	8	16
	9	60	1	.	.	9	15
	10	60	1	.	.	10	14
	11	60	1	0.542	0.102	11	13
	12	70	1	0.500	0.102	12	12
	13	90	1	0.458	0.102	13	11
	14	110	1	0.417	0.101	14	10
	15	120	1	.	.	15	9
	16	120	1	.	.	16	8
	17	120	1	0.292	0.093	17	7
	18	150	1	.	.	18	6
	19	150	1	.	.	19	5
	20	150	1	0.167	0.076	20	4
	21	180	1	.	.	21	3
	22	180	1	0.083	0.056	22	2
	23	300	1	0.042	0.041	23	1
	24	900	1	0.000	0.000	24	0
Zonnic 1.5 mg	1	30	1	0.958	0.041	1	23
	2	35	1	0.917	0.056	2	22
	3	40	1	0.875	0.068	3	21
	4	45	1	.	.	4	20
	5	45	1	.	.	5	19
	6	45	1	.	.	6	18
	7	45	1	.	.	7	17
	8	45	1	.	.	8	16
	9	45	1	.	.	9	15
	10	45	1	.	.	10	14
	11	45	1	0.542	0.102	11	13
	12	50	1	0.500	0.102	12	12
	13	55	1	0.458	0.102	13	11
	14	60	1	.	.	14	10
	15	60	1	0.375	0.099	15	9
	16	70	1	.	.	16	8
	17	70	1	0.292	0.093	17	7
	18	90	1	.	.	18	6
	19	90	1	0.208	0.083	19	5
	20	100	1	0.167	0.076	20	4
	21	105	1	0.125	0.068	21	3
	22	135	1	0.083	0.056	22	2
	23	150	1	.	.	23	1
	24	150	1	0.000	0.000	24	0

14.3 SAFETY DATA

All safety data are presented in Section 12.

15. REFERENCE LIST

1. Molyneux A**.** Nicotine replacement therapy. BMJ 2004;328:454-6.

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3. Usansky JI, Desai A, Tang-Liu D. PK Functions for Microsoft Excel Department of Pharmacokinetics and Drug Metabolism. Allergan, Irvine, CA 92606, U.S.A.

4. U.S. Department of Health and Human Services, Food and Drug Administration and Center for Drug Evaluation and Research (CDER). Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. January 2001.

5. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Controlled clinical trials 2, p 93-113, 1981.

16. APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

Enclosed.

16.1.2 Sample of case report form (unique pages only)

Enclosed.

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms

Enclosed.

16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Enclosed.

16.1.5 Signatures of principal or co-ordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

Enclosed.

16.1.6 Listing of patients receiving test drug(s)/ investigational product(s) from specific batches, where more than one batch was used

Not applicable since only one batch was used.

16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)

Enclosed.

16.1.8 Audit certificates (if available)

Enclosed.

16.1.9 Documentation of statistical methods

Enclosed.

16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

Not applicable.

16.1.11 Publications based on the study

Not applicable.

16.1.12 Important publications referenced in the report

Available on request.

16.2 PATIENT DATA LISTINGS

16.2.1 Discontinued patients

Not applicable since no patients discontinued prematurely.

16.2.2 Protocol deviations

A listing of ECO values is enclosed (no values >10 ppm). For PK sampling times, please see Appendix 16.2.5.

16.2.3 Patients excluded from the efficacy analysis

Not applicable.

16.2.4 Demographic data

Enclosed.

16.2.5 Compliance and/or drug concentration data (if available)

Enclosed.

16.2.6 Individual efficacy response data

Enclosed.

16.2.7 Adverse event listings (each patient)

Not applicable since no adverse events were reported.

16.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities.

A listing of vital signs is enclosed.

16.3 CASE REPORT FORMS

16.3.1 CRFs of deaths, other serious adverse events and withdrawals for AE

Not applicable since no serious adverse events or withdrawals for AEs were reported.

16.3.2 Other CRFs submitted

Not applicable.

16.4 INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)

Not included.