
Clinical Study Report

Investigational Product ZYN®
Study code SM 17-01
Report Version and date Final; 20 December 2018

The in vivo extraction of nicotine and flavor compounds from a single dose of a non-tobacco-based nicotine pouch (ZYN®) compared with conventional, tobacco-based Swedish snus among current, daily snus users

Study duration (FPI-LPO) 15 September 2017 – 14 November 2017

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This clinical study was conducted, and essential study documentation archived, in compliance with company SOPs and standards, which incorporate the requirements of the EU Clinical Studies Directive 2001/20/EC and ICH Guideline for Good Clinical Practice.

STUDY SYNOPSIS

Study Title	
The in vivo extraction of nicotine and flavor compounds from a single dose of a non-tobacco-based nicotine pouch (ZYN [®]) compared with conventional, tobacco-based Swedish snus among current, daily snus users	
Study code	
SM 17-01	
Study period	
Date of first subject screened: 15 September 2017 Date of last subject completed: 14 November 2017	
Principle Investigator	
	
Study center	
CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85 SE-751 85 Uppsala, Sweden	
Publication (reference)	
Not applicable.	
Study design	
Open, randomized, 14-way cross-over, single dose administration.	
Objectives	
<u>Primary objective</u>	
To compare the estimated in vivo extracted dose of nicotine from a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, respectively, with that from a 1 g Swedish snus pouch containing 8 mg of nicotine.	
<u>Secondary objectives</u>	
<ul style="list-style-type: none"> – Comparison of pulse rate as a surrogate endpoint, for systemic uptake of nicotine – Comparison of each subject's rating of subjective effect ("head buzz") and pulse rate – To estimate the in vivo extracted dose of flavor components to assess the overall flavor exposure from the non-tobacco-based nicotine pouch – Adverse event (AE) 	

Number of subjects

The planned number of subjects was 20. In total 25 subjects were screened and 20 subjects were enrolled into the study. Subjects were randomized to 1 of 4 treatment sequences (A-D), with 5 subjects in each sequence. All 5 subjects that were randomized to treatment sequence A, B and D, respectively, completed the study. Of the 5 subjects randomized to treatment sequence C, 3 subjects completed the study and 2 subjects were withdrawn. For treatment sequences, see the section Methodology below.

Diagnosis and main eligibility criteria

Healthy subjects aged ≥ 19 years who use tobacco-based snus since ≥ 1 year with a weekly consumption of 3 or more snus cans (brands with nicotine content $< 1\%$) or 2 or more cans (brands with nicotine content $> 1\%$). Subjects who were pregnant or who had a history of hypertension or any cardiovascular disease were excluded. Subjects shall be abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each trial day.

Methodology

Before entry to the study subjects underwent screening evaluations including medical history and pulse rate measurements before/after application of their usual brand of Swedish snus.

Subjects reported to the clinic on separate days for the 14 experimental sessions. The subjects were instructed to abstain from snus, cigarettes or other nicotine delivery products as from the evening before. All sessions were performed during the morning hours to facilitate abstinence. The subjects certified abstinence before each treatment was started.

The treatments were administered as single doses in a pre-determined randomized order. The subjects kept the pouch still between the upper lip and the gum for 15 or 60 min and were instructed not to manipulate the pouch with the tongue or lips. The subjects were instructed not to eat or drink from 30 min before and during dose administration.

Each used pouch was collected and frozen pending analyses of nicotine and flavor components. Unused pouches were collected and frozen pending analysis and served as references in the calculations of extracted doses.

The treatment sequences were:

Description of Element	Treatment Sequence A	Treatment Sequence B	Treatment Sequence C	Treatment Sequence D
	ZYN® Smooth 3 mg - 15 min	1	2	3
ZYN® Smooth 3 mg - 60 min	3	3	1	2
ZYN® Smooth 6 mg - 15 min	4	7	2	14
ZYN® Smooth 6 mg - 60 min	2	1	9	3
ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	5	4	4	12
ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	7	5	6	6
ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	8	6	7	7
ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	9	8	8	4
ZYN® Wintergreen 3 mg (Nicotine) - 60 min	6	10	10	9
ZYN® Wintergreen 3 mg (Flavor) - 60 min	10	13	12	10
ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	12	11	13	1
ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	13	12	14	11
Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	14	9	5	13
Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	11	14	11	5

Investigational Products (IPs), dosage and mode of administration, batch number

Test products:

- 1= ZYN® Smooth containing 3 mg nicotine per portion - 15 min administration, powder batch/batch number: 91153
- 2= ZYN® Smooth containing 3 mg nicotine per portion - 60 min administration, powder batch/batch number: 91153
- 3= ZYN® Smooth containing 6 mg nicotine per portion - 15 min administration, powder batch/batch number: 91250
- 4= ZYN® Smooth containing 6 mg nicotine per portion - 60 min administration, powder batch/batch number: 91250
- 5= ZYN® Smooth containing 3 mg nicotine per portion (alternative manufacturing process) – 15 min administration, powder batch/batch number: MG170908
- 6= ZYN® Smooth containing 3 mg nicotine per portion (alternative manufacturing process) – 60 min administration, powder batch/batch number: MG170908
- 7= ZYN® Smooth containing 6 mg nicotine per portion (alternative manufacturing process) – 15 min administration, powder batch/batch number: MG170830
- 8= ZYN® Smooth containing 6 mg nicotine per portion (alternative manufacturing process) – 60 min administration, powder batch/batch number: MG170830
- 9= ZYN® Wintergreen containing 3 mg nicotine per portion (nicotine analysis) - 60 min administration, powder batch/batch number: 91275
- 10= ZYN® Wintergreen containing 3 mg nicotine per portion (flavor analysis) - 60 min administration, powder batch/batch number: 91275

<p>11= ZYN[®] Peppermint containing 3 mg nicotine per portion (nicotine and flavor analysis) - 60 min administration, powder batch/batch number: 91087</p> <p>12= ZYN[®] Spearmint containing 3 mg nicotine per portion (nicotine and flavor analysis) - 60 min administration, powder batch/batch number: 91244</p> <p>Reference products:</p> <p>13= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) - 15 min administration, powder batch/batch number: 11081K6024</p> <p>14= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) - 60 min administration, powder batch/batch number: 11081K6024</p>
<p>Non-Investigational Products, dosage and mode of administration, batch number</p> <p>Not applicable.</p>
<p>Duration of treatment</p> <p>The treatments were administered as single doses in a pre-determined randomized order. The subjects kept the pouch still between the upper lip and the gum for 15 or 60 min.</p>
<p>Duration of subject's involvement in the study</p> <p>Each subject participated in the study for approximately 40-60 days. Two (2) subjects withdrew consent after 2 study treatments (completed Visit 3 and returned for the follow-up visit).</p>
<p>Efficacy assessments</p> <p>Extracted dose of nicotine - The extracted dose of nicotine from each portion was calculated by subtracting the residual amount after use from the mean of 10 unused portions.</p> <p>Vital signs – Pulse rate was measured before (0) and at 5, 10, 15, 30 and 60 min after each dose.</p> <p>Subjective effects – Each subject's rating of product "strength" using a visual analogue scale (VAS): (head "buzz", "head rush", "hit", feeling alert, overall "product strength"), anchored with "not at all" to "extremely" were obtained at preset time points up to 60 min after administration of each product.</p> <p>Extracted dose of flavor component - The extracted dose of flavor components was calculated.</p>
<p>Safety assessments</p> <p>Adverse events and serious adverse events (SAEs) were recorded from start of IP administration until the last follow-up visit. Medical events occurring between screening and first treatment with IP were reported separately as baseline events. Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA).</p>
<p>Statistical methods</p> <p>The primary endpoint was nicotine extraction. The study included 20 subjects. A previous study made the calculation of sample size possible. Nicotine extraction from a 1 g Swedish portion snus (PSWL) containing 8mg nicotine/pouch was estimated at 2.18 ± 0.92 mg per portion. Under the assumption of a complete dissolution and extraction of the 3 and 6 mg ZYN[®] products, respectively, versus the 2.18 ± 0.92 mg nicotine, and a standard deviation of 5.0 the estimated sample size was 16 with a power of 80% and $\alpha=0.05$. The randomization was performed using Latin Squares approach.</p> <p>Summary statistics was used to present all continuous variables and frequency tables for categorical variables. A significance level of 5% with 2-sided tests was used in all comparisons. The test products were compared to the 2 reference products in all analyses. In addition, pairwise comparisons between the test products were performed.</p>

The estimated in vivo extracted dose of nicotine from the non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, respectively, was compared with that from a 1 g Swedish snus pouch containing 8 mg of nicotine. The extracted dose of nicotine was analyzed using the Wilcoxon signed rank sum test and Student's t-test for within subject difference.

Pulse rate, VAS for "head buzz" and flavor extraction were analyzed using the Wilcoxon signed rank sum test and Student's t-test for within subject difference.

All AE data were fully listed by Investigator terms and MedDRA Preferred Term (PT). Adverse event data were summarized by System Organ Class (SOC) and PT.

EFFICACY RESULTS

Significant differences in the extracted dose of nicotine were observed after 15 and 60 min of administration between test products and Swedish portion snus PSWL 1.0 g (8 mg nicotine/g). The amount of nicotine extracted after 60 min was significantly higher in Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) compared to ZYN[®] 3 mg and significantly lower compared to ZYN[®] 6 mg. However, because of the large interindividual differences the ranges of extraction for the ZYN[®] products largely overlapped those of the reference products both at 15 and 60 min.

There was no evidence that extraction of nicotine was affected by the tested ZYN[®] flavorings or production technique. No significant difference in the extracted dose of nicotine was observed after 60 min of administration between any of the ZYN[®] 3 mg products independent of flavor compounds and no significant difference was observed after 15 and 60 min of administration between the ZYN[®] 3 mg or 6 mg products, respectively independent of production technique.

The rate of extraction for the ZYN[®] 3 mg or 6 mg products was significantly higher compared to the PSWL product.

There were no statistically significant differences in the change in pulse rate between each of the test products and the reference product at the majority of time points. Additionally, no significant difference in pulse rate was observed independently of flavor compounds or production technique. Pulse rate increased over time to a similar extent in all treatment groups; the median increase was, in general, equal to, or below, 10 beats/min.

The results of head buzz (measured by VAS) were not conclusive. There were no statistically significant differences in the change in head buzz between the test products and the reference product at the majority of time points during 15 min administration. Head buzz increased over time to a similar extent in all treatment groups. After 60 min administration, the increase was significantly larger for the reference product compared to ZYN[®] 3 mg and compared to the the flavored ZYN[®] products. Additionally, no significant difference in head buzz was observed independently of flavor compounds or production technique.

The mean \pm SD extracted doses of flavors from ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg, respectively were 1.5 ± 0.68 mg methylsalicylate (ZYN[®] Wintergreen 3 mg), 0.22 ± 0.13 mg menthol and 0.12 ± 0.06 mg menthone, respectively (ZYN[®] Peppermint 3 mg and 0.08 ± 0.04 mg menthol and 0.36 ± 0.18 mg carvone, respectively (ZYN[®] Spearmint 3 mg).

SAFETY RESULTS

Administration of single doses of nicotine-containing pouches was safe and well tolerated by the healthy subjects in this study. A total of 54 AEs was reported by 10 subjects during the study and 36 were judged to have a possible or probable relationship to treatment. The number of subjects reporting related AEs ranged from 1 to 5 during 11 of the 14 different treatments. Occasional AEs, mainly gastrointestinal disorders, were reported. There were no SAEs or discontinuations due to AEs during the study.

CONCLUSION

The extracted dose of nicotine was lower in the non-tobacco-based ZYN[®] 3 mg products compared to conventional, tobacco-based snus (PSWL) 8 mg. There were inconclusive results showing significant difference in pulse rate for some treatments. However, the difference was not highly associated with a larger increase in pulse rate or head buzz with PSWL treatment compared to treatment with ZYN[®] 3 mg.

Despite a lower nicotine content, the extracted dose of nicotine was higher in the ZYN[®] 6 mg products compared to the conventional, tobacco-based snus (PSWL) 8 mg product. The effect was not associated with a larger increase in pulse rate or a larger increase in head buzz with ZYN[®] 6 mg treatment compared to treatment with PSWL.

Different production technique and flavor compounds did not affect the extraction of nicotine from the test products.

The mean \pm SD extracted doses of flavors from ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg, respectively were 1.5 \pm 0.68 mg methylsalicylate (ZYN[®] Wintergreen 3 mg), 0.22 \pm 0.13 mg menthol and 0.12 \pm 0.06 mg menthone, respectively (ZYN[®] Peppermint 3 mg) and 0.08 \pm 0.04 mg menthol and 0.36 \pm 0.18 mg carvone, respectively (ZYN[®] Spearmint 3 mg).

Single doses of ZYN[®] products and the conventional, tobacco-based (PSWL) product administered during 15 and 60 min were well tolerated and no safety concerns were observed.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTC	CTC Clinical Trial Consultants AB
FAS	Full Analysis Set
FPI	First Patient In
GCP	Good Clinical Practice
h	Hour
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IQR	Interquartile range
LC/MS-MS	Liquid Chromatography-tandem Mass Spectrometry
LLOQ	Lower Limit of Quantification
LPO	Last Patient Out
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
N	Number
nmiss	Number of missing values
PPS	Per Protocol Set
PSWL	Pouched Snus White portion Large
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD/Std	Standard Deviation
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operating Procedures
TCA	Tricyclic Antidepressants
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
VAS	Visual Analogue Scale
WHO	World Health Organization

5 ETHICAL AND REGULATORY REQUIREMENTS

5.1 Ethical conduct of the study

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonization (ICH)/Good Clinical Practice (GCP), European Union Clinical Trials Directive, and applicable local regulatory requirements.

5.2 Ethics and regulatory review

The study did not start until approval of the Clinical Study Protocol (CSP), the Subject Information and the Informed Consent Forms (ICFs) had been obtained from the Independent Ethics Committee (IEC) in Uppsala, Sweden. It was the responsibility of the Investigator to forward a copy of the written approval and, where possible, a list of the members, their titles or occupations, and their institutional affiliations, to CTC Clinical Trial Consultants AB (CTC)/the Sponsor. The approval included a study identification and the date of review.

5.3 Subject information and consent

It was the responsibility of the Investigator or designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. The subjects were informed about their right to withdraw from the study at any time. Written subject information was given to each subject before enrolment. The written subject information was not to be changed without prior discussion with CTC/the Sponsor. All subjects were required to provide written informed consent prior to initiation of any study procedures. Furthermore, it was the responsibility of the Investigator or designee to obtain signed ICF from all subjects prior to inclusion in the study.

The signed ICFs were filed by the Investigator or designee for review by the Monitor. The Investigator confirmed receipt of the ICF from each subject by signing the appropriate page of the case report form (CRF).

The written Subject Information and ICF are included in Appendix 16.1.3.

5.4 Subject data protection

The Investigator kept a subject identification list not available to the Sponsor, including sufficient information to link records, i.e. CRFs and hospital records. The subjects were informed that the data were stored and analyzed by computer, that Swedish and local regulations for the handling of computerized data was followed and described in the written subject information and that identification of individual subject data was only possible for the Investigator. Furthermore, the subjects were informed about the possibility of inspection of relevant parts of the records by representatives of CTC and/or Authorities.

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Signatures required are included in Appendix 16.1.5.

7 INTRODUCTION

7.1 Project background

Sweden has the lowest prevalence of smoking in Europe, particularly among males. One explanation for the record-low smoking prevalence is that snus has replaced cigarettes as the tobacco product of choice among many male and some female smokers. Population surveys have also indicated that snus is the most frequently used smoking cessation aid. Snus is sometimes used as a last resort for people who have failed stopping smoking with the available, pharmaceutical smoking cessation aids. Smokeless tobacco is capable of rapidly delivering nicotine to the bloodstream (Fant et al 1999), and therefore may be more satisfactory among smokers than currently available pharmaceutical nicotine products. Traditionally there has been no non-tobacco-based nicotine product on the Swedish market intended for recreational use similar to Swedish snus. Despite the vast risk differential between snus and cigarettes in terms of adverse long-term health effects including cancer, cardiovascular disease and chronic lung disease, snus remains a controversial product as it contains tobacco and is intended for recreational use. The tobacco component of snus explains why it contains measurable amounts of unwanted constituents such as potentially carcinogenic nitrosamines, albeit at very low concentrations.

Recently, a novel, non-tobacco-based nicotine product (ZYN[®]) has been developed. It has some features that are similar to snus: it comes in pouches with a nicotine content of 3 or 6 mg; it is used the same way as snus, that is, it is placed under the upper lip. In contrast to snus the product contains no nitrosamines or polycyclic hydrocarbons which are the 2 main classes of unwanted substances in snus that are classified as potentially carcinogenic. Other unwanted substances in ZYN[®] are present in comparable or lower concentrations than in snus. The toxicological safety profile of ZYN[®] thus represents a significant improvement over snus with the exception of the nicotine content which is only marginally lower than in snus (3 or 6 mg in ZYN[®] versus e.g. 8-12 mg in a conventional 1.0 g snus pouch).

When comparing the nicotine content of different nicotine-containing products such as Swedish snus and Nicotine Replacement Therapy, it is important to consider that the nicotine extraction and uptake varies considerably depending on product type and formulation.

Commercially available snus products have a nicotine content ranging between 1-2%. Previous studies (Lunell E and Curvall M 2011), have indicated that on average about 15-20% of the total nicotine content is extracted and absorbed, with large inter-individual variation. Extraction is generally not linear with pouch size: it is larger with small compared to larger pouches, which suggests that surface area, saliva penetration and diffusion factors may be more important determinants of nicotine uptake than pouch weight. The nicotine delivery profile of a product is probably a main determinant of its efficacy to function as an alternative to cigarettes among current smokers. In view of these circumstances, it is highly justified to study the nicotine delivery profile of ZYN[®] in comparison with commercially available snus products (which have a documented ability to replace cigarettes as a source of recreational nicotine among current tobacco consumers). The Sponsor has previously conducted studies of nicotine chewing gum with different nicotine content versus snus products. The intention of this study was to extend those observations by comparing the ZYN[®] product with Swedish snus.

The current study was focused on the in vivo extraction of nicotine from ZYN[®] pouches versus a conventional snus pouch. Previous data indicated that the extracted amount of

nicotine from a snus pouch could be used as a proxy for systemic nicotine uptake (Erik Lunell, personal communication). This observation probably helps to explain the mentioned large inter-individual variation in nicotine uptake among snus users (which may be due to constitutional differences in saliva production). In contrast to a formal nicotine uptake study an in vivo extraction study does not involve invasive procedures. The extraction data will be supplemented with assessments of subjective effects of “product strength” and pulse rate measurements, both of which also constitute proxies for systemic nicotine uptake.

7.2 Investigational products

Test and reference products were delivered in identical containers labeled with unique identification numbers. The test product of non-tobacco-based nicotine contained 3 and 6 mg of nicotine, respectively, in a pouch. The reference product of 1 g Swedish snus pouch contained 8 mg of nicotine. Administration of the pouch was between the upper lip and the gum. For further details regarding the investigational products (IPs) used in this study, refer to Section 9.4.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective

To compare the estimated in vivo extracted dose of nicotine from a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, respectively, with that from a 1 g Swedish snus pouch containing 8 mg of nicotine.

8.1.1 Primary endpoint

The extracted dose of nicotine from each portion was calculated by subtracting the residual amount after use from the mean of 10 unused portions.

8.2 Secondary objectives

- Comparison of pulse rate as a surrogate endpoint, for systemic uptake of nicotine
- Comparison of each subject’s rating of subjective effect (“head buzz”) and pulse rate
- To estimate the in vivo extracted dose of flavor components to assess the overall flavor exposure from the non-tobacco-based nicotine pouch
- Adverse event (AE)

8.2.1 Secondary endpoints

- Pulse rate predose, +5 min, +10 min, +15 min, +30 min, +60 min after each dose
- Visual analogue scale (VAS) for measuring of "head buzz" (head rush, "hit", feeling alert, overall "product strength"), using a 100-mm VAS anchored with "not at all" to "extremely" at preset time points up to 60 min after study product administration (as a proxy for systemic uptake)
- The extracted dose of flavor components
- Collection of AE

9 INVESTIGATIONAL PLAN

9.1 Overall study design and schedule of events

The study was conducted as an open, randomized, 14-way cross-over, single dose administration. The study included 20 subjects.

The subjects included were healthy males and females aged >19 years who used tobacco-based snus since >1 year with a weekly consumption of 3 or more snus cans (brands with nicotine content <1%) or 2 or more cans (brands with nicotine content >1%). Subjects who were pregnant or who had a history of hypertension or any cardiovascular disease were excluded. Subjects were abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each trial day.

Before entry to the study, subjects underwent screening evaluations including smoking and snus use, medical history and pulse rate measurements before/after application of their usual brand of snus. A pulse increase of ≥ 10 beats/min in the morning before use of any nicotine containing product classified the subject as eligible for participation the study.

Subjects reported to the clinic on separate days (Visits 2 to 16) for the 14 experimental sessions. The subjects were instructed to abstain from snus, cigarettes or other nicotine delivery products as from 8 pm the evening before. All sessions were performed during the morning hours to facilitate abstinence. The subjects certified abstinence before each treatment was started.

The treatments were administered as single doses in a pre-determined randomized order. The subject kept the pouch still between the upper lip and the gum for 15 or 60 min and were instructed not to manipulate the pouch with the tongue or lips. The subjects were instructed not to eat or drink from 30 min before and during dose administration.

Each used pouch was collected and frozen pending analyses of nicotine and flavor components. Unused pouches were collected and frozen for analysis and served as references in the calculations of extracted doses.

Schedule of events is presented in Table 9.1-1.

Table 9.1-1 Overall schedule of events

Assessment	Screening	Cross-over phase	Follow-up Phone contact
	Visit 1 ¹ Day -14 to -1	Visit 2-15 ² Day 1 followed by 1-5 day(s) of wash-out. Repeated for each dose time point	Visit 16 7 days after last dose -3/+7 days
Informed consent	X		
Eligibility	X	X (re-check)	
Demographics	X		
Prior and concomitant medication	X	X	X
Medical history	X		
Urine pregnancy test ³	X		
Drug screen	X	X ⁴	
Pulse rate	X ⁵	X ⁶	
VAS		X ⁶	
IP administration		X	
Collection of pouches		X	
Baseline Symptoms	X		
AEs		X	X

1 Visit 1 could be performed during 2 days

2 See Detailed schedule of events for details, see Section 12.2 in the CSP (Appendix 16.1.1)

3 Female subjects only

4 Drug tests during the treatment period was performed randomly.

5 Before and 15 min after application of the subject's usual brand and amount of Swedish snus

6 Before and 5, 10, 15, 30 and 60 min after application of the IP

9.2 Rationale for study design and dose groups

The nicotine pharmacology of different pouched Swedish snus products has been extensively documented, most recently in a report by Lunell and Curvall (2011). The snus investigated in that report, Swedish portion snus: pouched snus white portion large (PSWL) 1.0 g (8 mg nicotine/g), released an average 2.18 mg nicotine following use over 30 min. Non-tobacco-based products with similar nicotine content were investigated in the present study. The rationale for the choice of the 3 mg and 6 mg dose of the non-tobacco-based nicotine pouch is that 6 mg proved safe in a previous study (Molander L and Lunell E 2001). In view of these circumstances, it is highly justified to study the nicotine delivery profile of the non-tobacco-based nicotine pouch (ZYN[®]) in comparison with commercially available snus products. Thus, the intention was to extend those observations by comparing a nicotine non-tobacco-based nicotine pouch (ZYN[®]) with Swedish snus.

9.3 Study population

9.3.1 Recruitment

The subjects were recruited from a list of healthy volunteers at CTC and from advertising in media.

9.3.2 **Number of subjects**

The study included 20 subjects.

9.3.3 **Inclusion criteria**

For inclusion in the study, subjects had to fulfill the following criteria:

1. Snus user, with a minimum weekly consumption of 3 or more snus cans (brands with nicotine content <1%) or 2 or more cans (brands with nicotine content >1%) since ≥ 1 year.
2. Consent to participate voluntarily and sign ICF prior to any study procedure.
3. Healthy male/female, aged ≥ 19 .
4. Willing and able to comply with study procedures.
5. A pulse increase ≥ 10 beats/min with first use of snus in the morning after overnight abstinence from any nicotine exposure.

9.3.4 **Exclusion criteria**

Subjects were not allowed to enter the study if any of the following exclusion criteria were fulfilled:

1. A history or presence of diagnosed hypertension or any cardiovascular disease.
2. Surgery within 6 months of the screening visit that, in the opinion of the investigator, could negatively impact on the subject's participation in the clinical study.
3. Any surgical or medical condition, which, in the judgment of the clinical investigator, could interfere with the absorption, distribution, metabolism or excretion of the drug.
4. Subjects who were pregnant.

9.3.5 **Restrictions during the study**

1. Subjects were abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each trial day.
2. The subjects were not allowed to eat, drink or use any other mouth related procedure (e.g. tooth brushing) 30 min before dose administration and for the duration of the study procedures (Henningfield JE et al 1990).
3. Other therapy considered necessary for the subject's welfare could be given at the discretion of the Investigator. All such therapy was recorded in the CRF.
4. Study subjects were not allowed to participate in any other clinical study during the study period.

9.3.6 **Criteria for subjects' withdrawal**

A subject could be withdrawn from the study treatment if, in the opinion of the Investigator, it was medically necessary, or if it was the wish of the subject. The reason for withdrawal was clearly described and the subject was, whenever possible, irrespective of the reason for withdrawal, medically examined as soon as possible. Relevant samples were obtained and all

relevant assessments were completed, preferably according to the schedule for the final assessment. The CRF were completed as far as possible.

9.3.6.1 Subject replacement

Subjects who were prematurely withdrawn from the study for any reason except the occurrence of treatment emergent adverse events (TEAEs) assessed as possibly or probably related to study treatment could be replaced during the course of the study.

9.3.6.2 Randomization

Subjects were assigned to the treatments using a computer-generated randomization list.

9.3.6.3 Blinding

The present study was an open, randomized study. Subjects were administered each dose by the personnel according to the randomization list.

9.4 Treatments

9.4.1 Identity of investigational product

Test products:

- 1= ZYN[®] Smooth containing 3 mg nicotine per portion - 15 min administration, powder batch/batch number: 91153
- 2= ZYN[®] Smooth containing 3 mg nicotine per portion - 60 min administration, powder batch/batch number: 91153
- 3= ZYN[®] Smooth containing 6 mg nicotine per portion - 15 min administration, powder batch/batch number: 91250
- 4= ZYN[®] Smooth containing 6 mg nicotine per portion - 60 min administration, powder batch/batch number: 91250
- 5= ZYN[®] Smooth containing 3 mg nicotine per portion (alternative manufacturing process) - 15 min administration, powder batch/batch number: MG170908
- 6= ZYN[®] Smooth containing 3 mg nicotine per portion (alternative manufacturing process) - 60 min administration, powder batch/batch number: MG170908
- 7= ZYN[®] Smooth containing 6 mg nicotine per portion (alternative manufacturing process) - 15 min administration, powder batch/batch number: MG170830
- 8= ZYN[®] Smooth containing 6 mg nicotine per portion (alternative manufacturing process) - 60 min administration, powder batch/batch number: MG170830
- 9= ZYN[®] Wintergreen containing 3 mg nicotine per portion (nicotine analysis) - 60 min administration, powder batch/batch number: 91275
- 10= ZYN[®] Wintergreen containing 3 mg nicotine per portion (flavor analysis) - 60 min administration, powder batch/batch number: 91275
- 11= ZYN[®] Peppermint containing 3 mg nicotine per portion (nicotine and flavor analysis) - 60 min administration, powder batch/batch number: 91087

12= ZYN® Spearmint containing 3 mg nicotine per portion (nicotine and flavor analysis) – 60 min administration, powder batch/batch number: 91244

Reference products:

13= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) (15 min administration), powder batch/batch number: 11081K6024

14= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) (60 min administration, powder batch/batch number: 11081K6024

9.4.2 Treatment administration

Each subject received single doses of the respective IP in the morning of each study day, see Table 9.4-1 for the treatment sequences to which the subjects were randomized.

Table 9.4-1 Definition of treatment sequences

Description of Element	Description of Arm (Treatment Group)			
	Treatment Sequence A	Treatment Sequence B	Treatment Sequence C	Treatment Sequence D
ZYN® Smooth 3 mg - 15 min	1	2	3	8
ZYN® Smooth 3 mg - 60 min	3	3	1	2
ZYN® Smooth 6 mg - 15 min	4	7	2	14
ZYN® Smooth 6 mg - 60 min	2	1	9	3
ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	5	4	4	12
ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	7	5	6	6
ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	8	6	7	7
ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	9	8	8	4
ZYN® Wintergreen 3 mg (Nicotine) - 60 min	6	10	10	9
ZYN® Wintergreen 3 mg (Flavor) - 60 min	10	13	12	10
ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	12	11	13	1
ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	13	12	14	11
Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	14	9	5	13
Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	11	14	11	5

SM17_01 treatment definitions, SAS program: treatment_definitions.sas.
Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-01-18T14:40:02

9.4.3 Treatment compliance

All IPs were administered at the research clinic under supervision of the clinical staff to ensure compliance.

9.5 Study assessments

9.5.1 Demographics and other baseline characteristics

9.5.1.1 Informed consent

Signed informed consent was obtained before any screening procedures were initiated. The informed consent procedure is further described in Section 5.3.

9.5.1.2 Demographic information

The following demographic data were recorded: gender, age and ethnic origin (race).

9.5.1.3 Medical/surgical history

Medical/surgical history was obtained by interview in order to verify that the eligibility criteria were met.

9.5.1.4 Urine drug screen

Urine was screened for drugs of abuse at screening using the Alere™ Drug Screen Test Panel. Additional random tests could be performed during the study period.

The following substances were included in the screen panel: Amphetamine, Barbiturates, Benzodiazepines, Buprenorphine, Clonazepam, Cocaine, Fentanyl, Ketamine, Marijuana (Tetrahydrocannabinol (THC)), Methadone, Methamphetamine, Methylenedioxymethamphetamine (MDMA), Morphine, Opiate, Oxycodone, Phencyclidine, Propoxyphene, Tramadol, Tricyclic antidepressants (TCA).

9.5.1.5 Pregnancy urine test

Pregnancy urine test was performed at the screening visit (females only).

9.5.1.6 Prior and concomitant medication

Prior medication, medication taken 2 weeks prior to screening, was obtained by interview and documented in the CRF.

Medications were classified as prior medications if the stop date was before or on the day of the first dose administration and as concomitant if ongoing at, and stopped after, the first dose administration, or started after the first dose administration.

Any use of concomitant medication from 2 weeks prior to screening until the last Follow-up Visit was documented in the CRF. Relevant information (i.e. name of medication, dose, unit, indication, reason for administration, dose form, frequency, route, start and stop dates) were recorded. All changes in medication were noted in the CRF.

9.5.1.7 Baseline symptoms

A baseline symptom was an event that occurred after a subject had signed the ICF up until the first administration of IP (i.e. during the screening period).

9.5.2 Assessments related to primary and secondary endpoints

9.5.2.1 Collection of pouches and analysis

Pouches for the determination of nicotine and flavors after administration of the IP were collected according to the instructions in the separate dosing instructions document at the pre-specified time-points. The following time windows applied for the pouch sampling:

- ± 1.5 min for all time-points

The date and time of collection of each pouch were recorded in the CRF.

All the collected pouches were collected and frozen immediately at -20°C. Pouches for extraction of nicotine and flavor were analyzed by Swedish Match. Pouches from all evaluable subjects excluding withdrawn or dropout subjects were analyzed.

9.5.2.2 Vital signs

Pulse rate was measured with an automatic device in sitting position after 10 min of rest.

9.5.2.3 Visual analogue scale

Visual analogue scale to measure "head buzz" (head rush, "hit", feeling alert, overall "product strength"), using a 100-mm VAS anchored with "not at all" to "extremely", was performed at preset time points up to 60 min after study product administration (as a proxy for systemic uptake).

9.5.3 Adverse events

Collection of baseline events started after the subject signs the ICF and continued until the first administration of IP. Collection of AEs started with administration of the IP (i.e. only TEAEs were collected and recorded in the CRF) and continued until the last follow-up assessment. Any AE with start date on the day of first IP administration were recorded with start time.

At the Follow-up Visit, information on new AEs or serious adverse events (SAEs), if any, and stop dates for AEs recorded and on-going during the dosing period were recorded.

All AEs were followed until they were resolved, or the subject's participation in the trial ended. In addition, all serious AEs and those non-serious events assessed by the investigator as possibly related to the investigational medication/product were followed even after the subject's participation in the trial was over. Such events were followed until they were resolved or until the Investigator assessed them as "chronic" or "stable". Resolution of such events was documented on the appropriate CRF.

The Investigator were to report SAEs to the Sponsor immediately (within 24 h) after becoming aware of them.

For detailed definition and reporting procedures, see Section 10 in the CSP (see Appendix 16.1.1).

9.5.4 Appropriateness of measurements

Measurements of nicotine extraction, pulse rate and use of a VAS are standard assessments in nicotine research. Standardized methods for measurements of safety and tolerability were used.

9.6 Data quality assurance

The study was performed in compliance with GCP, applicable regulations and CTC Standard Operating Procedures (SOPs).

Before inclusion of the first subject into the study, a study initiation visit was performed by a sponsor representative at the research clinic in order to inform and train relevant study staff. The Investigator was thereafter responsible for providing appropriate study related training to

new staff and to forward any new information of relevance to the performance of this study to the staff involved.

A CRF was completed for each subject included. A sample of the CRF is included as Appendix 16.1.2.

The study sites were periodically visited by a Monitor from CTC. The Monitor had direct access to hospital records and original data for Source Data Verification. For screening failures/non-included subjects, 100% source data verification (SDV) was performed for the Informed Consent procedure, demography (age and gender) and reason for non-inclusion. For all included subjects, protocol adherence and 100% SDV were performed for the Informed Consent procedure and all variables except prior and concomitant medications, urine dip-stick analysis, pulse rate, VAS and drug screen for which 100% SDV were performed on 5 subjects, randomly chosen.

All CRFs were reviewed for completion of recorded data, including missing data and inconsistencies in entered data.

9.7 Statistical methods planned in the protocol and determination of sample size

The statistical analyses performed in this study were initially specified in the CSP (see Appendix 16.1.1). Further details of the planned statistical analysis are provided in the Statistical Analysis Plan (SAP) (see Appendix 16.1.9.), which was finalized prior to the clean file meeting and database lock. Any changes in the SAP compared to the CSP are described in Section 9.8.2.

9.7.1 General

Continuous data are presented using summary statistics. Data are presented in terms of number (N), arithmetic mean, standard deviation (SD), median, minimum and maximum value.

Categorical data are presented as counts and percentages. When applicable, summary data are presented by treatment and by assessment time. Individual subject data are listed by subject number, treatment and, where applicable, by assessment time.

A significance level of 5% with 2-sided tests was used in all comparisons. The test products were compared to the reference products and in addition, pairwise comparisons between the test products were performed in the analyses (see Section 9.8.2).

9.7.2 Determination of sample size

The primary endpoint was nicotine extraction. The study included 20 subjects. A previous study (Lunell E & Curvall M 2011) made the calculation of sample size possible. Nicotine extraction from a 1 g Swedish portion snus (PSWL) containing 8 mg nicotine/pouch was estimated at 2.18 ± 0.92 mg per portion. Under the assumption of a complete dissolution and extraction of the 3 and 6 mg ZYN[®] products, respectively, versus the 2.18 ± 0.92 mg nicotine, and a standard deviation of 5.0 the estimated sample size is 16 with a power of 80% and $\alpha=0.05$. The randomization was performed using Latin Squares approach.

9.7.3 Definition of analysis data sets

The full analysis set (FAS) consists of all subjects who were randomized and have received at least 1 dose of IP. The per protocol analysis set (PPS) consists of all subjects who were

randomized, completed the study and had no major protocol violations. The baseline and safety data are presented using the FAS. All data regarding extraction of nicotine are presented using the PPS.

9.7.4 **Description of study population**

9.7.4.1 *Demographics and baseline characteristics*

The following baseline characteristics are summarized by treatment sequence: age, gender, ethnicity (race), pulse rate and pregnancy test.

9.7.4.2 *Medical history and concomitant medication*

Medical/surgical history and prior/concomitant medications are listed. Medical/surgical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications were coded according to World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) classification system.

9.7.4.3 *Treatment compliance*

Treatment compliance is listed.

9.7.5 **Analysis of primary endpoint**

The estimated in vivo extracted dose of nicotine from the non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, respectively, was compared with that from a 1 g Swedish snus pouch containing 8 mg of nicotine. The extracted dose of nicotine from each portion, were calculated by subtracting the residual amount after use from the mean of 10 unused portions.

The mean + SD extracted dose of nicotine from each pouch, was calculated. The extracted dose of nicotine was analyzed using the Wilcoxon signed rank sum test and Student's t-test (paired) for within subject difference.

9.7.6 **Analysis of secondary endpoints**

Pulse rate and VAS for "head buzz" were analyzed using the Wilcoxon signed rank sum test and Student's t-test (paired) for within subject difference.

The mean \pm SD extracted dose of flavors from each pouch, was calculated.

All AE data were fully listed by Investigator terms and MedDRA Preferred Term (PT). Adverse event data were summarized by System Organ Class (SOC) and PT.

Adverse events and baseline events were coded using MedDRA. The following summaries of AEs and SAEs are given by treatment and in total:

- Total number of AEs
- Total number of related AEs
- Total number (%) of subjects with at least 1 AE
- Total number (%) of subjects with at least 1 related AE
- AEs by MedDRA SOC and PT
- AEs by relation of study product and MedDRA SOC and PT

9.7.7 **Statistical/analytical issues**

9.7.7.1 *Adjustments for covariates*

No adjustments for covariates were performed.

9.7.7.2 *Handling of dropouts or missing data*

Missing data were not imputed.

9.7.7.3 *Significance level*

All tests were performed using 5% significance level.

9.7.7.4 *Multiple comparisons/multiplicity*

Even though many pairwise comparisons were made, no p-value adjustments were enforced. However, a medical/clinical judgement was applied to all significance tests, in order to avoid any conclusions based solely on statistical significance and without any clinical relevance.

9.7.7.5 *Examination of subgroups*

No subgroup analyses were performed.

9.8 **Changes in the conduct of the study or planned analyses**

There were no amendments made to the final CSP.

9.8.1 **Changes not described in a formal protocol amendment**

NA

9.8.2 **Changes in the planned statistical analyses**

The following analyses were not described in the CSP:

- Pairwise comparisons between the test products
- Analysis of the ratio of the extracted dose of nicotine (comparisons between test and the reference products and pairwise comparisons between the test products)
- Analysis of the rate of extraction of the dose of nicotine (comparisons between test and the reference products and pairwise comparisons between the test products)

The extracted dose of flavor was not compared between the different IPs or analyzed for within subject difference.

10 STUDY SUBJECTS

10.1 Disposition of subjects

10.1.1 Number of subjects

In total 25 subjects were screened and 20 subjects who fulfilled all inclusion criteria and none of the exclusion criteria were enrolled into the study. The reasons for non-inclusion are presented in Table 10.1-1. The first subject was enrolled on 15 September 2017, the first dose was administered on 18 September 2017 and the last subject completed the study on 14 November 2017.

Subjects were randomized to 1 of 4 treatment sequences (A-D), with 5 subjects in each sequence. All 5 subjects that were randomized to treatment sequence A, B and D, respectively, completed the study. Of the 5 subjects randomized to treatment sequence C, 3 subjects completed the study and 2 subjects were withdrawn. The disposition of subjects is shown in Figure 10.1-1. Summaries of study disposition and nicotine abstinence results are shown in Table 14.1-1 to Table 14.1-3 (Section 14.1). Individual subject data are provided in Appendices 16.2.1.

Figure 10.1-1 Disposition of subjects

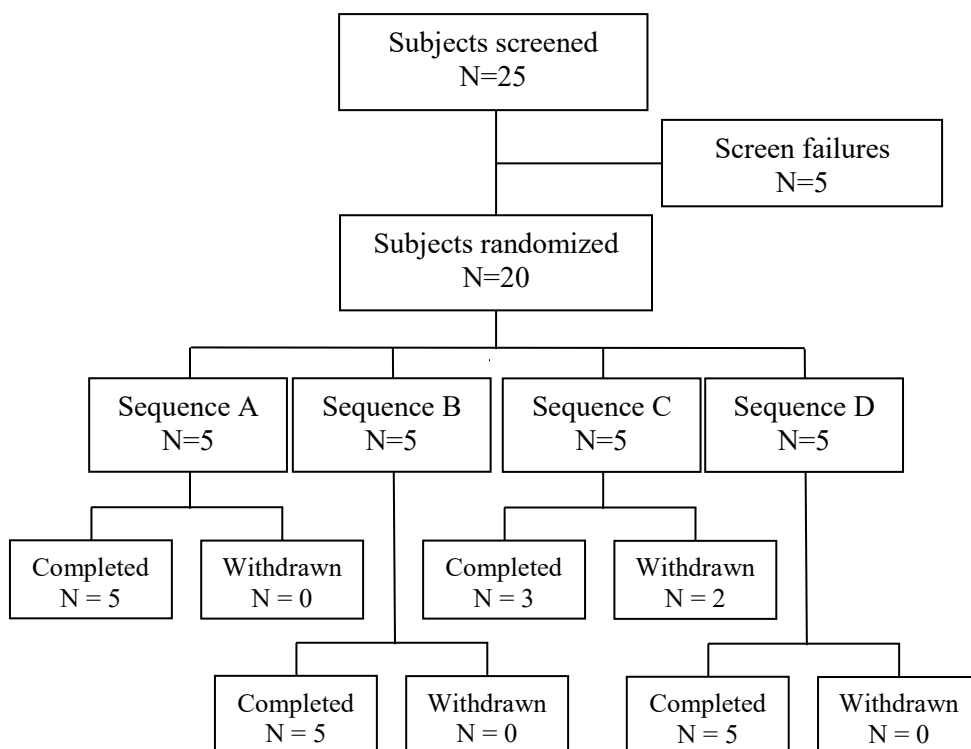


Table 10.1-1 Screen failures

Reason for non-inclusion	No of subjects
Screening failure	3
Not randomized	2
Total number	5

Source: Clean File Protocol SM 17-01, 11 Jan 2018

10.1.2 Study discontinuations

Of the 20 subjects enrolled, 2 subjects (Subjects 105 and 119) who were randomized to treatment sequence C withdrew their consent and ended the study after Visit 3 (i.e. after treatment with ZYN[®] Smooth 3 mg 60 min and ZYN[®] Smooth 6 mg 15 min).

10.2 Protocol deviations

There were no major deviations in the study. The minor protocol deviations that occurred were not considered to affect the evaluation of the study results. An individual listing of all protocol deviations is presented as Appendix 16.2.2.

10.3 Data sets analyzed

Twenty (20) subjects were included in FAS and 18 subjects were included in PPS (Table 10.3-1). Subjects 105 and 119 were excluded from the PPS due to withdrawal of consent (Appendix 16.2.3).

Table 10.3-1 Subjects included in the analysis sets

Subject number	FAS	PPS	Comment
101	1	1	
102	1	1	
103	1	1	
104	1	1	
105	1	0	Withdrawn consent
106	1	1	
107	1	1	
108	1	1	
109	1	1	
110	1	1	
111	1	1	
112	1	1	
113	1	1	
114	1	1	
115	1	1	
116	1	1	
117	1	1	
118	1	1	
119	1	0	Withdrawn consent
120	1	1	

1 = Included 0 = Not included

Source: Clean File Protocol SM 17-01, 11 Jan 2018

10.4 Demographics and other baseline characteristics

A total of 20 white subjects, 10 females and 10 males, were included in the study. The subjects had a mean (\pm SD) age of 29 \pm 9 years and a mean pulse of 68 \pm 10 beats/min at screening. All female subjects had a negative pregnancy test at screening. Demographic data are summarized by treatment sequence in Table 10.4-1 (FAS) and in Table 14.2-1 (PPS)

(Section 14.2). For definitions of the treatment sequences, refer to Table 9.4-1 in Section 9.4.2. Ten (10) subjects had a medical history of no clinical significance at the screening visit.

Individual subject demographic data, medical history and concomitant medications for all subjects randomized are presented in Appendix 16.2.4.

Table 10.4-1 Summary of demographic data and other baseline characteristics

		Treatment Sequence A (N=5)	Treatment Sequence B (N=5)	Treatment Sequence C (N=5)	Treatment Sequence D (N=5)	Total (N=20)
Age (years)	n/nmiss	5/0	5/0	5/0	5/0	20/0
	Mean (SD)	32.4 (13)	30.2 (4.44)	26.4 (11.6)	26 (3.46)	28.8 (8.83)
	Median (Min, Max)	28 (23, 55)	31 (23, 35)	22 (20, 47)	28 (20, 28)	28 (20, 55)
Gender	Female	4 (80%)	2 (40%)	3 (60%)	1 (20%)	10 (50%)
	Male	1 (20%)	3 (60%)	2 (40%)	4 (80%)	10 (50%)
Race	White	5 (100%)	5 (100%)	5 (100%)	5 (100%)	20 (100%)
Pulse (beats/min)	n/nmiss	5/0	5/0	5/0	5/0	20/0
	Mean (SD)	68 (7.11)	66.6 (9.96)	66.6 (14.2)	68.6 (9.94)	67.5 (9.77)
	Median (Min, Max)	69 (58, 75)	69 (53, 77)	74 (46, 80)	66 (61, 86)	67.5 (46, 86)
Pregnant at screening	Negative	4 (80%)	2 (40%)	3 (60%)	1 (20%)	10 (50%)
	Not Done	1 (20%)	3 (60%)	2 (40%)	4 (80%)	10 (50%)

SM17_01 summarized demographics data, SAS program: summary_demographics.sas.
Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-01-18T14:39:47

10.5 Measurements of treatment compliance

All IPs were administered at the research clinic under supervision by study staff to ensure compliance.

11 EVALUATION OF RESULTS

11.1 Extent of exposure

Pouches containing nicotine were administered as single doses. The subjects kept the pouch still between the upper lip and the gum for 15 or 60 min:

- 18 subjects received 8 single doses containing 3 mg nicotine, 4 single doses containing 6 mg nicotine and 2 single doses containing 8 mg nicotine
- 2 subjects received 1 single dose containing 3 mg nicotine and 1 single dose containing 6 mg nicotine

Individual exposure data are presented in Appendix 16.2.5.

11.2 Evaluation of primary endpoint

11.2.1 Extracted dose of nicotine

11.2.1.1 Comparison between test and reference products – extracted dose of nicotine

The Wilcoxon signed rank sum test showed statistically significant differences in extracted dose of nicotine after 15 min between the test products and the reference product, Table 11.2-1 to Table 11.2-4. The extracted dose from the test products containing 3 mg nicotine was significantly lower compared to the reference product. The extracted dose from the test products containing 6 mg was significantly higher compared to the reference product. The mean dose was 0.9 mg for the reference product compared to 0.4, 0.4, 1.1 and 1.0 mg for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively.

There were statistically significant differences in extracted dose of nicotine after 60 min between the test products and the reference product, Table 11.2-5 to Table 11.2-11. The extracted dose from the test products containing 3 mg nicotine was significantly lower compared to the reference product. The extracted the dose from the test products containing 6 mg was significantly higher compared to the reference product. The mean dose was 2.4 mg for the reference product compared to 1.6, 1.4, 3.5 and 3.4 mg for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg were 1.6, 1.5, 1.6 mg, respectively.

A linearity between 15 and 60 min seemed to be established for the reference and test products, see Figure 14.3-1 (Section 14.3.1). However, the individual variation between subjects was high for the 60 min assessment.

Summary statistics of extracted dose of nicotine are presented in Table 14.3-1 (Section 14.3). The distribution of extracted dose of nicotine is presented by product in Figure 14.3-1 (Section 14.3.1). Individual subject data are provided in Appendix 16.2.6.

Table 11.2-1 Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN[®] Smooth 3 mg - 15 min

Statistics	PSWL15	ZS315	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.1004
Mean (Std)	0.88 (1.19)	0.4 (0.16)	0.48 (1.17)	Signed Rank	0.0005
Median (min;max)	0.56 (0.32;5.54)	0.38 (0.18;0.71)	0.22 (-0.13;5.08)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.28 0.51 (0.23)	0.08 0.32 (0.24)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-2 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN[®] Smooth 6 mg - 15 min*

Statistics	PSWL15	ZS615	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.3217
Mean (Std)	0.88 (1.19)	1.08 (0.5)	-0.21 (0.86)	Signed Rank	0.0056
Median (min;max)	0.56 (0.32;5.54)	0.93 (0.5;2.52)	-0.4 (-1.37;3.02)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.83 1.14 (0.31)	-0.52 -0.24 (0.28)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-3 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min*

Statistics	PSWL15	ZS3A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0398
Mean (Std)	0.88 (1.19)	0.4 (0.3)	0.47 (0.9)	Signed Rank	<.0001
Median (min;max)	0.56 (0.32;5.54)	0.34 (0.14;1.55)	0.23 (0.01;3.99)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.29 0.4 (0.11)	0.09 0.45 (0.36)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-4 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min*

Statistics	PSWL15	ZS6A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.7538
Mean (Std)	0.88 (1.19)	0.95 (0.47)	-0.08 (1.03)	Signed Rank	0.0385
Median (min;max)	0.56 (0.32;5.54)	0.81 (0.5;2.04)	-0.28 (-1.25;3.77)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.64 1.06 (0.42)	-0.44 0.01 (0.45)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-5 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 3 mg - 60 min*

Statistics	PSWL60	ZS360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.58 (0.51)	0.81 (0.61)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.61 (0.79;2.36)	0.68 (0;1.84)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.14 1.95 (0.81)	0.38 1.41 (1.03)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-6 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 6 mg - 60 min*

Statistics	PSWL60	ZS660	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	3.54 (1.15)	-1.15 (0.83)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	3.44 (1.54;5.6)	-1.22 (-2.45;0.6)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	2.8 4.3 (1.5)	-1.58 -0.78 (0.8)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-7 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min*

Statistics	PSWL60	ZS3A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.41 (0.56)	0.99 (0.47)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.28 (0.63;2.69)	0.96 (0.08;1.72)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.05 1.84 (0.79)	0.76 1.43 (0.67)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-8 *Difference in extracted dose of (mg) nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min*

Statistics	PSWL60	ZS6A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0012
Mean (Std)	2.39 (0.82)	3.42 (1.31)	-1.03 (1.12)	Signed Rank	0.0008
Median (min;max)	2.24 (1.23;4.04)	3.46 (1.07;5.33)	-1.01 (-2.96;1.07)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	2.35 4.58 (2.23)	-1.7 -0.25 (1.45)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-9 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Wintergreen 3 mg - 60 min*

Statistics	PSWL60	SW360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.58 (0.46)	0.82 (0.46)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.48 (0.93;2.41)	0.86 (-0.05;1.78)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.28 1.89 (0.61)	0.51 1.04 (0.53)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-10 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Peppermint 3 mg - 60 min*

Statistics	PSWL60	ZP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.53 (0.52)	0.86 (0.53)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.51 (0.53;2.31)	0.82 (0.05;1.73)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.16 1.87 (0.71)	0.46 1.32 (0.86)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

Table 11.2-11 *Difference in extracted dose (mg) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Spearmint 3 mg- 60 min*

Statistics	PSWL60	ZSP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.63 (0.54)	0.77 (0.43)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.44 (0.88;2.85)	0.85 (-0.2;1.29)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.24 1.96 (0.72)	0.41 1.14 (0.73)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:38:11

11.2.1.2 *Pairwise comparison between test products – extracted dose of nicotine*

There were no statistically significant differences in extracted dose of nicotine between ZYN[®] Smooth 3 mg and 6 mg compared to ZYN[®] Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 min or administered during 60 min, see Table 14.3-2 to Table 14.3-5 (Section 14.3.1).

There were no statistically significant differences between ZYN[®] Smooth 3 mg compared to ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg or ZYN[®] Spearmint 3 mg administered during 60 min, see Table 14.3-6 to Table 14.3-8 (Section 14.3.1).

11.2.1.3 *Comparison between test and reference products – extracted dose of nicotine (ratio)*

The analyses of the ratio of extracted dose of nicotine showed statistically significant differences between the 15 min test products and the reference product, see Table 11.2-12 to Table 11.2-15. The analysis of the ratio of extracted dose of nicotine showed statistically significant differences between the 60 min test products and the reference product, see Table 11.2-16 to Table 11.2-22.

Table 11.2-12 *Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 3 mg - 15 min*

Statistics	PSWL15	ZS315	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0520
Mean (Std)	0.88 (1.19)	0.4 (0.16)	2.23 (2.51)	Signed Rank	0.0004
Median (min;max)	0.56 (0.32;5.54)	0.38 (0.18;0.71)	1.63 (0.76;11.94)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.28 0.51 (0.23)	1.16 2.26 (1.1)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-13 *Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 6 mg - 15 min*

Statistics	PSWL15	ZS615	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0108
Mean (Std)	0.88 (1.19)	1.08 (0.5)	0.71 (0.43)	Signed Rank	0.0056
Median (min;max)	0.56 (0.32;5.54)	0.93 (0.5;2.52)	0.55 (0.37;2.2)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.83 1.14 (0.31)	0.46 0.71 (0.25)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-14 *Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min*

Statistics	PSWL15	ZS3A15	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0002
Mean (Std)	0.88 (1.19)	0.4 (0.3)	1.98 (0.9)	Signed Rank	<.0001
Median (min;max)	0.56 (0.32;5.54)	0.34 (0.14;1.55)	1.72 (1.03;4.35)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.29 0.4 (0.11)	1.35 2.56 (1.21)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-15 *Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min*

Statistics	PSWL15	ZS6A15	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.3737
Mean (Std)	0.88 (1.19)	0.95 (0.47)	0.86 (0.64)	Signed Rank	0.0342
Median (min;max)	0.56 (0.32;5.54)	0.81 (0.5;2.04)	0.67 (0.36;3.13)		
Q1, Q3 (IQR)	0.43 0.79 (0.36)	0.64 1.06 (0.42)	0.51 1.01 (0.5)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-16 *Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 3 mg - 60 min*

Statistics	PSWL60	ZS360	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0002
Mean (Std)	2.39 (0.82)	1.58 (0.51)	1.59 (0.54)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.61 (0.79;2.36)	1.35 (1;3.03)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.14 1.95 (0.81)	1.25 1.83 (0.58)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-17 Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 6 mg - 60 min

Statistics	PSWL60	ZS660	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	3.54 (1.15)	0.71 (0.23)	Signed Rank	0.0005
Median (min;max)	2.24 (1.23;4.04)	3.44 (1.54;5.6)	0.7 (0.43;1.39)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	2.8 4.3 (1.5)	0.54 0.81 (0.27)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-18 Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min

Statistics	PSWL60	ZS3A60	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.41 (0.56)	1.8 (0.53)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.28 (0.63;2.69)	1.7 (1.07;3.21)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.05 1.84 (0.79)	1.5 2.08 (0.58)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-19 Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min

Statistics	PSWL60	ZS6A60	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0262
Mean (Std)	2.39 (0.82)	3.42 (1.31)	0.79 (0.37)	Signed Rank	0.0034
Median (min;max)	2.24 (1.23;4.04)	3.46 (1.07;5.33)	0.73 (0.29;2)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	2.35 4.58 (2.23)	0.58 0.88 (0.3)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-20 Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. - ZYN[®] Wintergreen 3 mg - 60 min

Statistics	PSWL60	SW360	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.58 (0.46)	1.52 (0.26)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.48 (0.93;2.41)	1.57 (0.96;1.8)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.28 1.89 (0.61)	1.43 1.75 (0.32)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-21 Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Peppermint 3 mg - 60 min

Statistics	PSWL60	ZP360	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0005
Mean (Std)	2.39 (0.82)	1.53 (0.52)	1.66 (0.66)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.51 (0.53;2.31)	1.61 (1.03;4.05)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.16 1.87 (0.71)	1.26 1.78 (0.52)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 11.2-22 Ratio of extracted dose of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Spearmint 3 mg - 60 min

Statistics	PSWL60	ZSP360	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	2.39 (0.82)	1.63 (0.54)	1.49 (0.26)	Signed Rank	<.0001
Median (min;max)	2.24 (1.23;4.04)	1.44 (0.88;2.85)	1.49 (0.88;1.93)		
Q1, Q3 (IQR)	1.76 3.1 (1.34)	1.24 1.96 (0.72)	1.32 1.63 (0.31)		

SM17_01 Analysis of primary endpoint RATIO, SAS program: Primary_endpoint_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

11.2.1.4 Pairwise comparison between the test products – extracted dose of nicotine (ratio)

The analyses of the ratio of extracted dose of nicotine showed statistically significant differences between ZYN[®] Smooth 3 mg and 3 mg (alternative manufacturing process) administered during 60 min and between ZYN[®] Smooth 6 mg and 6 mg (alternative manufacturing process) administered during 15 min, see Table 14.3-9 to Table 14.3-12 (Section 14.3.1). However, compared to Section 11.2.1.2 these results are inconclusive.

The analyses of the ratio of extracted dose of nicotine showed no statistically significant differences between ZYN[®] Smooth 3 mg and ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg, respectively, administered during 60 min, see Table 14.3-13 to Table 14.3-15 (Section 14.3.1).

11.2.1.5 Comparison between test and reference products – extracted dose of nicotine (rate of extraction)

The Wilcoxon signed rank sum test showed statistically significant differences in rate of extraction between the test products and the reference product administered during 15 min and 60 min, see Table 11.2-23 to Table 11.2-33. The rate of extraction for the test products was significantly higher compared to the reference product.

The mean rate of extraction for the reference product administered during 15 min was 11.6% compared to 13.1, 14.5, 17.1 and 17.3% for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively.

The mean rate of extraction for the reference product administered during 60 min was 31.7% compared to 52.1, 50.6, 56.0 and 61.9% for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg were 51.7, 49.5, 52.6%, respectively.

Table 11.2-23 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN® Smooth 3 mg - 15 min*

Statistics	PSWL15	ZS315	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.6767
Mean (Std)	11.58 (15.53)	13.12 (5.06)	-1.53 (15.34)	Signed Rank	0.0040
Median (min;max)	7.46 (4.24;72.44)	12.65 (5.87;23.11)	-3.41 (-12.11;57.43)		
Q1, Q3 (IQR)	5.69 10.76 (5.07)	9.07 17.12 (8.05)	-7.84 -1.76 (6.08)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-24 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN® Smooth 6 mg - 15 min*

Statistics	PSWL15	ZS615	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0438
Mean (Std)	11.58 (15.53)	17.06 (7.85)	-5.48 (10.68)	Signed Rank	0.0019
Median (min;max)	7.46 (4.24;72.44)	14.57 (7.85;39.44)	-7.44 (-23.29;33)		
Q1, Q3 (IQR)	5.69 10.76 (5.07)	13.09 17.45 (4.36)	-8.96 -5.53 (3.43)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-25 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min*

Statistics	PSWL15	ZS3A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0394
Mean (Std)	11.58 (15.53)	14.5 (11.05)	-2.92 (5.55)	Signed Rank	0.0090
Median (min;max)	7.46 (4.24;72.44)	12.1 (4.7;56.52)	-4.82 (-7.87;15.92)		
Q1, Q3 (IQR)	5.69 10.76 (5.07)	10.51 14.36 (3.85)	-6.34 -1.42 (4.92)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-26 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 15 min vs. ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min*

Statistics	PSWL15	ZS6A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0846
Mean (Std)	11.58 (15.53)	17.33 (8.45)	-5.75 (13.32)	Signed Rank	0.0019
Median (min;max)	7.46 (4.24;72.44)	14.49 (8.96;36.96)	-7.66 (-26.2;40.34)		
Q1, Q3 (IQR)	5.69 10.76 (5.07)	11.66 19.3 (7.64)	-9.46 -2.39 (7.07)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-27 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 3 mg - 60 min*

Statistics	PSWL60	ZS360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	31.73 (10.8)	52.14 (17.12)	-20.41 (12.88)	Signed Rank	<.0001
Median (min;max)	29.19 (16.23;52.76)	52.57 (26.14;79.52)	-21.09 (-44.61;6.15)		
Q1, Q3 (IQR)	23.53 40.56 (17.03)	37.19 64.65 (27.46)	-29.15 -10.96 (18.19)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-28 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 6 mg - 60 min*

Statistics	PSWL60	ZS660	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	31.73 (10.8)	55.98 (18.08)	-24.25 (13.13)	Signed Rank	<.0001
Median (min;max)	29.19 (16.23;52.76)	53.4 (24.18;90.42)	-23.55 (-43.78;4.17)		
Q1, Q3 (IQR)	23.53 40.56 (17.03)	44.63 67.21 (22.58)	-34.84 -16.51 (18.33)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-29 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min*

Statistics	PSWL60	ZS3A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	31.73 (10.8)	50.57 (20.37)	-18.84 (13.13)	Signed Rank	<.0001
Median (min;max)	29.19 (16.23;52.76)	46.32 (22.62;98.15)	-17.85 (-45.39;5.18)		
Q1, Q3 (IQR)	23.53 40.56 (17.03)	38.44 65.95 (27.51)	-29.32 -13 (16.32)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-30 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min*

Statistics	PSWL60	ZS6A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	31.73 (10.8)	61.93 (23.66)	-30.2 (20.05)	Signed Rank	<.0001
Median (min;max)	29.19 (16.23;52.76)	62.9 (19.31;96.15)	-29.11 (-59.61;9.04)		
Q1, Q3 (IQR)	23.53 40.56 (17.03)	42.19 83.14 (40.95)	-46.05 -12.75 (33.3)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-31 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Wintergreen 3 mg - 60 min*

Statistics	PSWL60	SW360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	31.73 (10.8)	51.69 (15.51)	-19.96 (7.51)	Signed Rank	<.0001
Median (min;max)	29.19 (16.23;52.76)	48.26 (29.63;79.92)	-21.46 (-33.29;-9.16)		
Q1, Q3 (IQR)	23.53 40.56 (17.03)	42.08 62.57 (20.49)	-25.69 -12.49 (13.2)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-32 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Peppermint 3 mg - 60 min*

Statistics	PSWL60	ZP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	31.73 (10.8)	49.49 (16.89)	-17.76 (10.99)	Signed Rank	0.0001
Median (min;max)	29.19 (16.23;52.76)	47.99 (17.02;75.56)	-22.13 (-34.15;11.33)		
Q1, Q3 (IQR)	23.53 40.56 (17.03)	38.43 60.77 (22.34)	-24.31 -10.97 (13.34)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 11.2-33 *Difference in rate of extraction (%) of nicotine: Swedish portion snus PSWL 1.0 g (8 mg) – 60 min vs. ZYN[®] Spearmint 3 mg - 60 min*

Statistics	PSWL60	ZSP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
Mean (Std)	31.73 (10.8)	52.64 (17.51)	-20.91 (9.63)	Signed Rank	<.0001
Median (min;max)	29.19 (16.23;52.76)	46.53 (28.57;91.98)	-19.24 (-39.22;-7.35)		
Q1, Q3 (IQR)	23.53 40.56 (17.03)	40.29 63.17 (22.88)	-28.32 -15.59 (12.73)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

11.2.1.6 *Pairwise comparison between the test products – extracted dose of nicotine (rate of extraction)*

There were no statistically significant differences in rate of extraction between ZYN[®] Smooth 3 mg and 6 mg compared to ZYN[®] Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 min or administered during 60 min, see Table 14.3-16 to Table 14.3-19 (Section 14.3.1).

There were no statistically significant differences between ZYN[®] Smooth 3 mg compared to ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg or ZYN[®] Spearmint 3 mg administered during 60 min, see Table 14.3-20 to Table 14.3-22 (Section 14.3.1).

11.3 **Evaluation of secondary endpoints**

11.3.1 **Vital signs**

11.3.1.1 *Comparison between the test and reference products – pulse rate*

There were no statistically significant differences in change in pulse rate at the majority of time points between the test products and the reference product administered during 15 min, see Table 14.3-24 to Table 14.3-27 (Section 14.3.2). Pulse rate changed over time to a similar extent in all treatment groups. The median change from baseline at 15 min was 7 beats/min for the reference product compared to 7, 5, 10 and 9.5 beats/min for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively.

There were no statistically significant differences in change in pulse rate at the majority of time points between test products and the reference product administered during 60 min, except for a significant higher pulse rate in the reference product compared to most ZYN[®]

3 mg treatments at 10 min, see Table 14.3-28 to Table 14.3-35 (Section 14.3.2). Pulse rate increased over time to a similar extent in all treatment groups. The median change from baseline at 15 min was 6.5 beats/min for the reference product compared to 3.5, 3, 6.5 and 8 beats/min for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN[®] Wintergreen 3 mg (nicotine), ZYN[®] Wintergreen 3 mg (flavor), ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg were 6, 3, 4 and 4.5 beats/min, respectively. The median change from baseline at 60 min was 7 beats/min for the reference product compared to 5, 2.5, 6 and 7 beats/min for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN[®] Wintergreen 3 mg (nicotine), ZYN[®] Wintergreen 3 mg (flavor), ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg were 3.5, 6, 3 and 8 beats/min, respectively.

Descriptive statistics are presented in Table 14.3-23 (Section 14.3.2). Individual subject data are provided in Appendix 16.2.6.

11.3.1.2 *Pairwise comparison between the test products – pulse rate*

There were no statistically significant differences between ZYN[®] Smooth 3 mg and 6 mg compared to ZYN[®] Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 min or administered during 60 min, see Table 14.3-36 to Table 14.3-39 (Section 14.3.2).

There were no statistically significant differences between ZYN[®] Smooth 3 mg compared to ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg or ZYN[®] Spearmint 3 mg administered during 60 min, see Table 14.3-40 to Table 14.3-42 (Section 14.3.2).

11.3.2 *Visual analogue scale*

11.3.2.1 *Comparison between the test and reference products – VAS*

There were no statistically significant differences in change in head buzz (measured by VAS) between the test products and the reference product administered during 15 min, see Table 14.3-44 to Table 14.3-47 (Section 14.3.2). Head buzz changed over time to a similar extent in all treatment groups. The median change from baseline at 15 min was 6.5 for the reference product compared to 5.5, 5, 7 and 4 for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively.

There was a statistically significant difference at 60 min between ZYN[®] Smooth 3 mg and the reference product administered during 60 min, see Table 14.3-48 (Section 14.3.2). The change in head buzz was significantly smaller compared to the reference product. There were no statistically significant differences between ZYN[®] Smooth 6 mg, ZYN[®] Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process) compared to the reference product administered during 60 min, see Table 14.3-49 to Table 14.3-51 (Section 14.3.2).

There were statistically significant differences at 60 min between ZYN[®] Wintergreen 3 mg (nicotine), ZYN[®] Wintergreen 3 mg (flavor), ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg compared to the reference product administered during 60 min, see Table 14.3-52, Table 14.3-54 and Table 14.3-55 (Section 14.3.2), respectively. In addition, there were also statistically significant differences at time points between 10 min and up to 60 min between ZYN[®] Wintergreen 3 mg (flavor) and ZYN[®] Spearmint 3 mg compared to the reference

product administered during 60 min, see Table 14.3-53 and Table 14.3-55 (Section 14.3.2), respectively. The changes were significantly smaller compared to the reference product.

The median change from baseline at 15 min was 10.5 for the reference product compared to 7.5, 3, 10.5 and 6.5 for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN[®] Wintergreen 3 mg (nicotine), ZYN[®] Wintergreen 3 mg (flavor), ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg were 5.5, 4.5, 5.5 and 4, respectively. The median change from baseline at 60 min was 1.5 for the reference product compared to 0, 0, 4 and 0.5 for ZYN[®] 3 mg, ZYN[®] 3 mg (alternative manufacturing process), ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process), respectively. The corresponding value for ZYN[®] Wintergreen 3 mg (nicotine), ZYN[®] Wintergreen 3 mg (flavor), ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg was 0 for all treatments.

Descriptive statistics are presented in Table 14.3-43 (Section 14.3.2). Individual subject data are provided in Appendix 16.2.6.

11.3.2.2 Pairwise comparison between the test products – VAS

There were no statistically significant differences between ZYN[®] Smooth 3 mg and 6 mg compared to ZYN[®] Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 min or administered during 60 min, see Table 14.3-56 to Table 14.3-59 (Section 14.3.2).

There were no statistically significant differences between ZYN[®] Smooth 3 mg compared to ZYN[®] Wintergreen 3 mg or ZYN[®] Peppermint 3 mg administered during 60 min, see Table 14.3-60 and Table 14.3-61 (Section 14.3.2), respectively. There was a statistically significant difference in change in head buzz at 60 min between ZYN[®] Smooth 3 mg and ZYN[®] Spearmint 3 mg administered during 60 min, see Table 14.3-62 (Section 14.3.2). The change was significantly larger for ZYN[®] Smooth 3 mg compared to ZYN[®] Spearmint 3 mg, however the change was only 1 mm which is considered not clinically relevant.

11.3.3 Dose of flavor

The mean (\pm SD) extracted dose of methylsalicylate was 1.5 ± 0.68 mg from ZYN[®] Wintergreen 3 mg. The mean (\pm SD) extracted doses of menthol and menthone were 0.22 ± 0.13 mg and 0.12 ± 0.06 mg, respectively from ZYN[®] Peppermint 3 mg. The mean (\pm SD) extracted doses of menthol and carvone were 0.08 ± 0.04 mg and 0.36 ± 0.18 mg, respectively from ZYN[®] Spearmint 3 mg. Descriptive statistics of the extracted dose of flavor are presented in Table 14.3-63 (Section 14.3.2). In addition, summary statistics of flavors and nicotine are found in Table 14.3-1 (Section 14.3). Individual subject data are provided in Appendix 16.2.6.

11.3.4 Adverse events

See Section 12.

11.4 Statistical/analytical issues

Not applicable.

11.5 Summary of efficacy results

Significant differences in the extracted dose of nicotine were observed after 15 and 60 min of administration between test products and Swedish portion snus PSWL 1.0 g (8 mg nicotine/g). The amount of nicotine extracted after 60 min was significantly higher in Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) compared to ZYN[®] 3 mg and significantly lower compared to ZYN[®] 6 mg. However, because of the large interindividual differences the ranges of extraction for the ZYN[®] products largely overlapped those of the reference products both at 15 and 60 min.

There was no evidence that extraction of nicotine was affected by the tested ZYN[®] flavorings or production technique. No significant difference in the extracted dose of nicotine was observed after 60 min of administration between any of the ZYN[®] 3 mg products independent of flavor compounds and no significant difference was observed after 15 and 60 min of administration between the ZYN[®] 3 mg or 6 mg products, respectively independent of production technique.

The rate of extraction for the ZYN[®] 3 mg or 6 mg products was significantly higher compared to the PSWL product.

There were no statistically significant differences in the change in pulse rate between each of the test products and the reference product at the majority of time points. Additionally, no significant difference in pulse rate was observed independently of flavor compounds or production technique. Pulse rate increased over time to a similar extent in all treatment groups; the median increase was, in general, equal to, or below, 10 beats/min.

The results of head buzz (measured by VAS) were not conclusive. There were no statistically significant differences in the change in head buzz between the test products and the reference product at the majority of time points, after 15 min administration. Head buzz increased over time to a similar extent in all treatment groups. After 60 min administration, the increase was significantly larger for the reference product compared to ZYN[®] 3 mg and compared to the the flavored ZYN[®] products. Additionally, no significant difference in head buzz was observed independently of flavor compounds or production technique.

The mean \pm SD extracted doses of flavors from ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg, respectively were 1.5 \pm 0.68 mg methylsalicylate (ZYN[®] Wintergreen 3 mg), 0.22 \pm 0.13 mg menthol and 0.12 \pm 0.06 mg menthone, respectively (ZYN[®] Peppermint 3 mg and 0.08 \pm 0.04 mg menthol and 0.36 \pm 0.18 mg carvone, respectively (ZYN[®] Spearmint 3 mg).

12 ADVERSE EVENTS

12.1 Brief summary of adverse events

A total of 54 AEs was reported during the study, ranging from 1 to 10 during all treatments but 2 (ZYN[®] Smooth 3 mg (alternative manufacturing process) - 15 min and Swedish portion snus PSWL 1.0 g - 15 min). Ten (10) subjects did not report any AEs and the number of subjects reporting AEs during the different treatments ranged from 1 to 5. Thirty-six (36) of the AEs were judged to have a possible or probable relationship to treatment. The number of subjects with at least 1 related AE during the different treatments ranged from 0 to 5.

There were no SAEs or withdrawals due to AEs.

A summary of treatment-emergent AEs in total and by treatment is presented in Table 12.1-1. Summaries of number of subjects with at least 1 AE and number of subjects with at least 1 related AE are presented in Table 12.1-2 and Table 12.1-3, respectively.

Table 12.1-1 Treatment emergent AEs: Number of AE both total and by treatment

Treatment	Number of AE:s
Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	0
Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	3
ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	7
ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	0
ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	5
ZYN® Smooth 3 mg - 15 min	1
ZYN® Smooth 3 mg - 60 min	5
ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	2
ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	2
ZYN® Smooth 6 mg - 15 min	2
ZYN® Smooth 6 mg - 60 min	10
ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	10
ZYN® Wintergreen 3 mg (Flavor) - 60 min	4
ZYN® Wintergreen 3 mg (Nicotine) - 60 min	3
Total	54

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Table 12.1-2 Treatment emergent AEs: Number of subjects with at least 1 AE, by treatment

Treatment	AE	No AE
Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	0	18
Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	3	15
ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	5	13
ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	0	18
ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	4	14
ZYN® Smooth 3 mg - 15 min	1	17
ZYN® Smooth 3 mg - 60 min	4	16
ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	2	16
ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	2	16
ZYN® Smooth 6 mg - 15 min	2	18
ZYN® Smooth 6 mg - 60 min	5	13
ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	5	13
ZYN® Wintergreen 3 mg (Flavor) - 60 min	3	15
ZYN® Wintergreen 3 mg (Nicotine) - 60 min	2	16

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Table 12.1-3 Treatment emergent AEs: Number of subjects with at least 1 related AE, by treatment

Treatment	Number of subjects with no related AE		Number of subjects with at least one related AE	
	n	%	n	%
Swedish portion snus PSWL 1.0 g (8 mg) - 15 min		0.0%		0.0%
Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	1	33.3%	2	66.7%
ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	2	40.0%	3	60.0%
ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min		0.0%		0.0%
ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	2	50.0%	2	50.0%
ZYN® Smooth 3 mg - 15 min	1	100.0%		0.0%
ZYN® Smooth 3 mg - 60 min	2	50.0%	2	50.0%
ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	1	50.0%	1	50.0%
ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min		0.0%	2	100.0%
ZYN® Smooth 6 mg - 15 min	1	50.0%	1	50.0%
ZYN® Smooth 6 mg - 60 min		0.0%	5	100.0%
ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	3	60.0%	2	40.0%
ZYN® Wintergreen 3 mg (Flavor) - 60 min		0.0%	3	100.0%
ZYN® Wintergreen 3 mg (Nicotine) - 60 min	1	50.0%	1	50.0%

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12.2 Display of adverse events

Gastrointestinal disorders were reported during all 12 treatments. Salivary hypersecretion was reported during 9 treatments by 1 (5.6%) to 3 (16.7%) subjects. Dry mouth was reported by 1 (5.6%) subject during 5 treatments. Nasopharyngitis was reported during 4 treatments by 1 (5.6%) to 2 (16.7%) subjects. All other AEs were reported during 1 to 2 treatments.

The number and percentage of subjects who had at least 1 AE are presented by SOC in Table 12.2-1 and by SOC and PT in Table 12.2-2 and Table 12.2-3 (by relation to study product).

Table 12.2-1 Treatment emergent AEs: Subject unique AEs by MedDRA body class

Body System or Organ Class	Treatment											
	Swedish portion snus PSWL 1.0 g (8 mg) - 60 min		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 3 mg - 15 min		ZYN® Smooth 3 mg - 60 min		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	
	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects
Gastrointestinal disorders	1	5.6%	2	11.1%	2	11.1%	1	5.6%	2	10.0%	1	5.6%
General disorders and administration site conditions			1	5.6%								
Infections and infestations	1	5.6%	1	5.6%					1	5.0%	1	5.6%
Musculoskeletal and connective tissue disorders			1	5.6%	1	5.6%						
Nervous system disorders	1	5.6%	1	5.6%					1	5.0%		
Psychiatric disorders					1	5.6%						

Body System or Organ Class	Treatment											
	ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 6 mg - 15 min		ZYN® Smooth 6 mg - 60 min		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Wintergreen 3 mg (Flavor) - 60 min		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	
	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects
Gastrointestinal disorders	2	11.1%	1	5.0%	4	22.2%	3	16.7%	3	16.7%	1	5.6%
General disorders and administration site conditions			1	5.0%	1	5.6%	1	5.6%				
Infections and infestations							1	5.6%				
Musculoskeletal and connective tissue disorders							1	5.6%				
Nervous system disorders					1	5.6%	1	5.6%			1	5.6%
Psychiatric disorders												

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Table 12.2-2 Treatment emergent AEs: Subject unique AEs by MedDRA body class and PT

Body System or Organ Class	Dictionary-Derived Term	Treatment											
		Swedish portion snus PSQL 1.0 g (8 mg) - 60 min		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 3 mg - 15 min		ZYN® Smooth 3 mg - 60 min		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	
		Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects
Gastrointestinal disorders	Abdominal pain upper												
	Dry mouth					1	5.6%			1	5.0%	1	5.6%
	Dyspepsia												
	Gingival pain									1	5.0%		
	Nausea							1	5.6%				
	Salivary hypersecretion	1	5.6%	2	11.1%	1	5.6%			1	5.0%		
	Throat irritation												
	Tongue discomfort			1	5.6%	1	5.6%						
	Vomiting												
General disorders and administration site conditions	Feeling cold												
	Hunger			1	5.6%								
	Pyrexia												
Infections and infestations	Nasopharyngitis	1	5.6%	1	5.6%					1	5.0%	1	5.6%
Musculoskeletal and connective tissue disorders	Pain in extremity							1	5.6%				
	Pain in jaw			1	5.6%								
Nervous system disorders	Dizziness			1	5.6%								
	Headache									1	5.0%		
	Hypoaesthesia	1	5.6%										
Psychiatric disorders	Insomnia							1	5.6%				

Body System or Organ Class	Dictionary-Derived Term	Treatment											
		ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 6 mg - 15 min		ZYN® Smooth 6 mg - 60 min		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Wintergreen 3 mg (Flavor) - 60 min		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	
		Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects
Gastrointestinal disorders	Abdominal pain upper							1	5.6%				
	Dry mouth			1	5.0%	1	5.6%						
	Dyspepsia					2	11.1%	1	5.6%				
	Gingival pain												
	Nausea	1	5.6%										
	Salivary hypersecretion	1	5.6%			3	16.7%	2	11.1%	3	16.7%	1	5.6%
	Throat irritation					1	5.6%					1	5.6%
	Tongue discomfort							1	5.6%	1	5.6%		
	Vomiting							1	5.6%				
General disorders and administration site conditions	Feeling cold			1	5.0%	1	5.6%						
	Hunger												
	Pyrexia							1	5.6%				
Infections and infestations	Nasopharyngitis							1	5.6%				
Musculoskeletal and connective tissue disorders	Pain in extremity							1	5.6%				
	Pain in jaw												
Nervous system disorders	Dizziness												
	Headache					1	5.6%	1	5.6%			1	5.6%
	Hypoaesthesia												
Psychiatric disorders	Insomnia												

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Table 12.2-3 Treatment emergent AEs: Subject unique AEs by relation to study product and MedDRA body class and PT

Body System or Organ Class	Dictionary-Derived Term	Causality	Treatment											
			Swedish portion snus PSWL 1.0 g (8 mg) - 60 min		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 3 mg - 15 min		ZYN® Smooth 3 mg - 60 min		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	
			Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects
Gastrointestinal disorders	Abdominal pain upper	NOT RELATED												
	Dry mouth	POSSIBLE									1	5.0%		
		PROBABLE			1	5.6%							1	5.6%
	Dyspepsia	POSSIBLE												
		PROBABLE												
	Gingival pain	POSSIBLE									1	5.0%		
	Nausea	NOT RELATED							1	5.6%				
		PROBABLE												
	Salivary hypersecretion	PROBABLE	1	5.6%	2	11.1%	1	5.6%			1	5.0%		
	Throat irritation	PROBABLE												
	Tongue discomfort	POSSIBLE						1	5.6%					
		PROBABLE			1	5.6%								
	Vomiting	NOT RELATED												
General disorders and administration site conditions	Feeling cold	NOT RELATED												
		POSSIBLE												
	Hunger	POSSIBLE			1	5.6%								
	Pyrexia	NOT RELATED												
Infections and infestations	Nasopharyngitis	NOT RELATED	1	5.6%	1	5.6%					1	5.0%	1	5.6%
Musculoskeletal and connective tissue disorders	Pain in extremity	NOT RELATED						1	5.6%					
	Pain in jaw	NOT RELATED			1	5.6%								

Body System or Organ Class	Dictionary-Derived Term	Causality	Treatment											
			Swedish portion snus PSWL 1.0 g (8 mg) - 60 min		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 3 mg - 15 min		ZYN® Smooth 3 mg - 60 min		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	
			Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects
Nervous system disorders	Dizziness	PROBABLE			1	5.6%								
	Headache	NOT RELATED									1	5.0%		
		PROBABLE												
Psychiatric disorders	Hypoaesthesia	PROBABLE	1	5.6%										
	Insomnia	NOT RELATED					1	5.6%						

Body System or Organ Class	Dictionary-Derived Term	Causality	Treatment												
			ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 6 mg - 15 min		ZYN® Smooth 6 mg - 60 min		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Wintergreen 3 mg (Flavor) - 60 min		ZYN® Wintergreen 3 mg (Nicotine) - 60 min		
			Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	
Gastrointestinal disorders	Abdominal pain upper	NOT RELATED							1	5.6%					
	Dry mouth	POSSIBLE			1	5.0%									
		PROBABLE					1	5.6%							
	Dyspepsia	POSSIBLE					2	11.1%							
		PROBABLE							1	5.6%					
	Gingival pain	POSSIBLE													
	Nausea	NOT RELATED													
		PROBABLE		1	5.6%										
	Salivary hypersecretion	PROBABLE		1	5.6%			3	16.7%	2	11.1%	3	16.7%	1	5.6%
	Throat irritation	PROBABLE						1	5.6%					1	5.6%
Gastrointestinal disorders	Tongue discomfort	POSSIBLE													
		PROBABLE							1	5.6%	1	5.6%			
	Vomiting	NOT RELATED							1	5.6%					
		PROBABLE													
General disorders and administration site conditions	Feeling cold	NOT RELATED			1	5.0%									
		POSSIBLE						1	5.6%						
	Hunger	POSSIBLE													
	Pyrexia	NOT RELATED							1	5.6%					
Infections and infestations	Nasopharyngitis	NOT RELATED							1	5.6%					
Musculoskeletal and connective tissue disorders	Pain in extremity	NOT RELATED							1	5.6%					
	Pain in jaw	NOT RELATED													

Body System or Organ Class	Dictionary-Derived Term	Causality	Treatment											
			ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min		ZYN® Smooth 6 mg - 15 min		ZYN® Smooth 6 mg - 60 min		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min		ZYN® Wintergreen 3 mg (Flavor) - 60 min		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	
			Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects	Number of subjects	% of subjects
Nervous system disorders	Dizziness	PROBABLE												
	Headache	NOT RELATED					1	5.6%	1	5.6%			1	5.6%
		PROBABLE					1	5.6%						
	Hypoaesthesia	PROBABLE												
Psychiatric disorders	Insomnia	NOT RELATED												

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12.3 Analysis of adverse events

Seven (7) subjects reported 36 AEs with a probable or possible relationship with IP during the study. Salivary hypersecretion with a probable relationship was reported during 9 treatments by 1 (5.6%) to 3 (16.7%) subjects. Dry mouth with a probable or possible relationship was reported by 1 (5.6%) subject during 5 treatments. All other related AEs were reported during 1 to 3 treatments. The causality of the rest of the reported AEs were assessed as “not related” by the investigator. All AEs were resolved at the study end.

There was no obvious difference in the number of subjects reporting AEs, number of AEs or types of AEs between treatments. Overall the number of subjects reporting AEs, and the number of AEs, was low.

12.4 Listing of adverse events by subject

Adverse events are listed by subject in Appendix 16.2.7.

12.5 Deaths, other serious adverse events and other significant adverse events

There were no deaths, other SAEs or other significant AEs during the study, see Table 14.4-1 and Table 14.4-2 (Section 14.4.1).

12.6 Summary of safety results

Administration of single doses of nicotine-containing pouches was safe and well tolerated by the healthy subjects in this study. A total of 54 AEs was reported by 10 subjects during the study and 36 were judged to have a possible or probable relationship to treatment. The number of subjects reporting related AEs ranged from 1 to 5 during 11 of the 14 different treatments. Occasional AEs, mainly gastrointestinal disorders, were reported. There were no SAEs or discontinuations due to AEs during the study.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

This open, randomized, 14-way cross-over study compared the extracted dose of nicotine and subjective effects of nicotine following a single dose of a non-tobacco-based nicotine pouch (ZYN[®]) containing either 3 mg (non-flavored and flavored pouches) or 6 mg nicotine and a single dose of conventional, tobacco-based Swedish snus (PSWL) containing 8 mg nicotine in 20 daily snus users. Two different manufacturing processes of ZYN[®] 3 mg and 6 mg were also compared.

The main aim of the study was to document the in vivo extraction of nicotine from ZYN[®] pouches versus a conventional snus pouch. The extraction was supplemented with assessments of subjective effects of “product strength” and pulse rate measurements, both of which constitute proxies for systemic nicotine uptake. The extracted dose of flavor components to assess the overall flavor exposure from the ZYN[®] products was also estimated.

The extraction of nicotine from Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) was higher compared to ZYN[®] 3 mg and ZYN[®] 3 mg (alternative manufacturing process) independent of flavor compounds. However, the extraction of nicotine from ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process) was higher than Swedish portion snus PSWL 1.0 g (8 mg nicotine/g).

The extraction of nicotine, in relation to the total dose of nicotine in the pouch, seemed to be higher in the ZYN[®] products compared to Swedish portion snus PSWL 1.0 g (8 mg nicotine/g). This could be explained by the geometry of the ZYN[®] pouch which would lead to a more efficient saliva penetration of the pouch.

A linearity between 15 and 60 min seemed to be established for the Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) and the ZYN[®] products. However, the individual variation between subjects was high for the 60 min assessment.

The repeated measurements of pulse rate and head buzz (measured by VAS) during 60 min did not show conclusive results. Pulse rate increase was slightly higher for ZYN[®] 6 mg products than for ZYN[®] 3 mg products at the end of 15 min administration and the 60 min administration. The increase was similar for the flavored ZYN[®] products. The increase was similar also at 15 min for the 60 min administration, thus the increase in pulse rate was maintained up to the end of administration. The differences were however, not statistically significant.

Head buzz increase was similar for ZYN[®] 6 mg products and ZYN[®] 3 mg products at the end of 15 min and at 15 min during the 60 min administration. The increase was similar for the flavored ZYN[®] products. As opposed to pulse rate, the increase in head buzz was not maintained up to the end of the 60 min administration. The increase at 15 min declined during the 60 min administration.

13.2 OVERALL CONCLUSIONS

The extracted dose of nicotine was lower in the non-tobacco-based ZYN[®] 3 mg products compared to conventional, tobacco-based snus (PSWL) 8 mg. There were inconclusive results showing significant difference in pulse rate for some treatments. However, the difference in extracted dose was not highly associated with a larger increase in pulse rate or head buzz with PSWL treatment compared to treatment with ZYN[®] 3 mg.

Despite a lower nicotine content, the extracted dose of nicotine was higher in the ZYN[®] 6 mg products compared to the conventional, tobacco-based snus (PSWL) 8 mg product. The effect was not associated with a larger increase in pulse rate or a larger increase in head buzz with ZYN[®] 6 mg treatment compared to treatment with PSWL.

Different production technique and flavor compounds did not affect the extraction of nicotine from the test products.

The mean \pm SD extracted doses of flavors from ZYN[®] Wintergreen 3 mg, ZYN[®] Peppermint 3 mg and ZYN[®] Spearmint 3 mg, respectively were 1.5 ± 0.68 mg methylsalicylate (ZYN[®] Wintergreen 3 mg), 0.22 ± 0.13 mg menthol and 0.12 ± 0.06 mg menthone, respectively (ZYN[®] Peppermint 3 mg) and 0.08 ± 0.04 mg menthol and 0.36 ± 0.18 mg carvone, respectively (ZYN[®] Spearmint 3 mg).

Single doses of ZYN[®] products and the conventional, tobacco-based (PSWL) product administered during 15 and 60 min were well tolerated and no safety concerns were observed.

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

14.1 Study subjects

Table 14.1-1 Study disposition (completed and withdrawn subjects)

Completed according to protocol?	Description of Planned Arm			
	Treatment Sequence A	Treatment Sequence B	Treatment Sequence C	Treatment Sequence D
	COMPLETED	5	5	3
WITHDRAWAL OF CONSENT			2	

SM17_01 DS disposition data, SAS program: subject_disposition.sas.

Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-01-18T14:39:40

Table 14.1-2 Number of subjects per visit

Visit Name	Description of Planned Arm			
	Treatment Sequence A	Treatment Sequence B	Treatment Sequence C	Treatment Sequence D
	Study Start	5	5	5
Screening	5	5	5	5
Visit 2	5	5	5	5
Visit 3	5	5	5	5
Visit 4	5	5	3	5
Visit 5	5	5	3	5
Visit 6	5	5	3	5
Visit 7	5	5	3	5
Visit 8	5	5	3	5
Visit 9	5	5	3	5
Visit 10	5	5	3	5
Visit 11	5	5	3	5
Visit 12	5	5	3	5
Visit 13	5	5	3	5
Visit 14	5	5	3	5
Visit 15	5	5	3	5
Visit 16 Follow-up	5	5	3	5
Visit 17 End of Study	5	5	5	5

SM17_01 SV disposition data, SAS program: subject_disposition.sas.

Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-01-18T14:39:40

Table 14.1-3 Nicotine abstinence

Name of Actual Treatment	Abstinence result
	Yes
Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	18
Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	18
ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	18
ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	18
ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	18
ZYN® Smooth 3 mg - 15 min	18
ZYN® Smooth 3 mg - 60 min	18
ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	18
ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	18
ZYN® Smooth 6 mg - 15 min	18
ZYN® Smooth 6 mg - 60 min	18
ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	18
ZYN® Wintergreen 3 mg (Flavor) - 60 min	18
ZYN® Wintergreen 3 mg (Nicotine) - 60 min	18

SM17_01 QS disposition data, SAS program: subject_disposition.sas.

Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-01-18T14:39:40

14.2 Demographic data and other baseline characteristics

Table 14.2-1 Summary of demographic data and other baseline characteristics (PPS)

		Treatment Sequence A (N=5)	Treatment Sequence B (N=5)	Treatment Sequence C (N=3)	Treatment Sequence D (N=5)	Total (N=18)
Age (years)	n/nmiss	5/0	5/0	3/0	5/0	18/0
	Mean (SD)	32.4 (13)	30.2 (4.44)	30 (14.8)	26 (3.46)	29.6 (8.9)
	Median (Min, Max)	28 (23, 55)	31 (23, 35)	23 (20, 47)	28 (20, 28)	28 (20, 55)
Gender	Female	4 (80%)	2 (40%)	2 (67%)	1 (20%)	9 (50%)
	Male	1 (20%)	3 (60%)	1 (33%)	4 (80%)	9 (50%)
Race	White	5 (100%)	5 (100%)	3 (100%)	5 (100%)	18 (100%)
Pulse (beats/min)	n/nmiss	5/0	5/0	3/0	5/0	18/0
	Mean (SD)	68 (7.11)	66.6 (9.96)	59.7 (14.6)	68.6 (9.94)	66.4 (9.68)
	Median (Min, Max)	69 (58, 75)	69 (53, 77)	58 (46, 75)	66 (61, 86)	66 (46, 86)
Pregnant at screening	Negative	4 (80%)	2 (40%)	2 (67%)	1 (20%)	9 (50%)
	Not Done	1 (20%)	3 (60%)	1 (33%)	4 (80%)	9 (50%)

SM17_01 summarized demographics data, SAS program: summary_demographics_PPS.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-16T13:39:19

14.3 Primary and secondary endpoints

Table 14.3-1 Summary statistics of laboratory measurements by treatment

Laboratory test name	Result Category	Treatment	N	Min	Max	Mean	Median	Std
Carvone (mg)	Measured value	ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	18	0.164	0.845	0.363	0.338	0.176
Menthol (mg)	Measured value	ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	18	0.0109	0.561	0.221	0.209	0.126
		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	18	0.0107	0.173	0.0758	0.0635	0.0414
Menthone (mg)	Measured value	ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	18	0.0151	0.273	0.117	0.11	0.064
Methylsalicylate (mg)	Measured value	ZYN® Wintergreen 3 mg (Flavor) - 60 min	18	0.655	3.14	1.5	1.25	0.679
Nicotine (mg)	Measured value	Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	18	0.321	5.54	0.876	0.558	1.19
		Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	18	1.23	4.04	2.39	2.24	0.818
		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	18	0.529	2.31	1.53	1.51	0.52
		ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	18	0.135	1.55	0.403	0.338	0.302
		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	18	0.629	2.69	1.41	1.28	0.557
		ZYN® Smooth 3 mg - 15 min	18	0.178	0.713	0.399	0.381	0.156
		ZYN® Smooth 3 mg - 60 min	18	0.792	2.36	1.58	1.61	0.511
		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	18	0.495	2.04	0.954	0.806	0.466
		ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	18	1.07	5.33	3.42	3.46	1.31
		ZYN® Smooth 6 mg - 15 min	18	0.504	2.52	1.08	0.925	0.502
		ZYN® Smooth 6 mg - 60 min	18	1.54	5.6	3.54	3.44	1.15
		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	18	0.881	2.85	1.63	1.44	0.545
		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	18	0.926	2.41	1.58	1.48	0.462

SM17_01 LB tabulations, SAS program: safety_tabulations.sas.

Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:36:14

14.3.1 Primary endpoint

Table 14.3-2 Difference in extracted dose (mg) of nicotine (pairwise): ZYN® Smooth 3 mg - 15 min vs. ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min

Statistics	ZS315	ZS3A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.9447
Mean (Std)	0.4 (0.16)	0.4 (0.3)	0 (0.29)	Signed Rank	0.1708
Median (min;max)	0.38 (0.18;0.71)	0.34 (0.14;1.55)	0.07 (-1.09;0.27)		
Q1, Q3 (IQR)	0.28 0.51 (0.23)	0.29 0.4 (0.11)	-0.03 0.14 (0.17)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-22T10:57:24

Table 14.3-3 Difference in extracted dose (mg) of nicotine (pairwise): ZYN® Smooth 3 mg - 60 min vs. ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min

Statistics	ZS360	ZS3A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0666
Mean (Std)	1.58 (0.51)	1.41 (0.56)	0.17 (0.37)	Signed Rank	0.0898
Median (min;max)	1.61 (0.79;2.36)	1.28 (0.63;2.69)	0.14 (-0.41;0.91)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.05 1.84 (0.79)	-0.14 0.43 (0.57)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-22T10:57:24

Table 14.3-4 *Difference in extracted dose (mg) of nicotine (pairwise): ZYN[®] Smooth 6 mg - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min*

Statistics	ZS615	ZS6A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.1384
Mean (Std)	1.08 (0.5)	0.95 (0.47)	0.13 (0.36)	Signed Rank	0.0432
Median (min;max)	0.93 (0.5;2.52)	0.81 (0.5;2.04)	0.17 (-0.88;0.75)		
Q1, Q3 (IQR)	0.83 1.14 (0.31)	0.64 1.06 (0.42)	-0.02 0.34 (0.36)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-22T10:57:24

Table 14.3-5 *Difference in extracted dose (mg) of nicotine (pairwise): ZYN[®] Smooth 6 mg - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min*

Statistics	ZS660	ZS6A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.5957
Mean (Std)	3.54 (1.15)	3.42 (1.31)	0.12 (0.93)	Signed Rank	0.6705
Median (min;max)	3.44 (1.54;5.6)	3.46 (1.07;5.33)	0.29 (-1.38;1.97)		
Q1, Q3 (IQR)	2.8 4.3 (1.5)	2.35 4.58 (2.23)	-0.75 0.81 (1.56)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-22T10:57:24

Table 14.3-6 *Difference in extracted dose (mg) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Wintergreen 3 mg - 60 min*

Statistics	ZS360	SW360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.9895
Mean (Std)	1.58 (0.51)	1.58 (0.46)	0 (0.42)	Signed Rank	1.0000
Median (min;max)	1.61 (0.79;2.36)	1.48 (0.93;2.41)	0.04 (-0.76;0.88)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.28 1.89 (0.61)	-0.35 0.3 (0.65)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-22T10:57:24

Table 14.3-7 *Difference in extracted dose (mg) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Peppermint 3 mg - 60 min*

Statistics	ZS360	ZP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.6496
Mean (Std)	1.58 (0.51)	1.53 (0.52)	0.04 (0.41)	Signed Rank	0.3634
Median (min;max)	1.61 (0.79;2.36)	1.51 (0.53;2.31)	0.06 (-0.75;0.98)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.16 1.87 (0.71)	-0.06 0.27 (0.33)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-22T10:57:24

Table 14.3-8 *Difference in extracted dose (mg) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Spearmint 3 mg - 60 min*

Statistics	ZS360	ZSP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.6984
Mean (Std)	1.58 (0.51)	1.63 (0.54)	-0.05 (0.52)	Signed Rank	0.6171
Median (min;max)	1.61 (0.79;2.36)	1.44 (0.88;2.85)	-0.05 (-0.94;1)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.24 1.96 (0.72)	-0.49 0.28 (0.77)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-22T10:57:24

Table 14.3-9 *Ratio of extracted dose of nicotine (pairwise): ZYN[®] Smooth 3 mg - 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min*

Statistics	ZS315	ZS3A15	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.1465
Mean (Std)	0.4 (0.16)	0.4 (0.3)	1.15 (0.43)	Signed Rank	0.0987
Median (min;max)	0.38 (0.18;0.71)	0.34 (0.14;1.55)	1.15 (0.3;2.07)		
Q1, Q3 (IQR)	0.28 0.51 (0.23)	0.29 0.4 (0.11)	0.92 1.3 (0.38)		

SM17_01 Analysis of primary endpoint Ratio, SAS program: Primary_endpoint_pairwise_extra_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 14.3-10 *Ratio of extracted dose of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min*

Statistics	ZS360	ZS3A60	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0237
Mean (Std)	1.58 (0.51)	1.41 (0.56)	1.18 (0.31)	Signed Rank	0.0342
Median (min;max)	1.61 (0.79;2.36)	1.28 (0.63;2.69)	1.13 (0.73;1.81)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.05 1.84 (0.79)	0.9 1.37 (0.47)		

SM17_01 Analysis of primary endpoint Ratio, SAS program: Primary_endpoint_pairwise_extra_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 14.3-11 *Ratio of extracted dose of nicotine (pairwise): ZYN[®] Smooth 6 mg - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min*

Statistics	ZS615	ZS6A15	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.0283
Mean (Std)	1.08 (0.5)	0.95 (0.47)	1.21 (0.38)	Signed Rank	0.0237
Median (min;max)	0.93 (0.5;2.52)	0.81 (0.5;2.04)	1.2 (0.51;2.14)		
Q1, Q3 (IQR)	0.83 1.14 (0.31)	0.64 1.06 (0.42)	0.98 1.42 (0.44)		

SM17_01 Analysis of primary endpoint Ratio, SAS program: Primary_endpoint_pairwise_extra_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 14.3-12 *Ratio of extracted dose of nicotine (pairwise): ZYN[®] Smooth 6 mg - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min*

Statistics	ZS660	ZS6A60	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.1639
Mean (Std)	3.54 (1.15)	3.42 (1.31)	1.1 (0.3)	Signed Rank	0.2288
Median (min;max)	3.44 (1.54;5.6)	3.46 (1.07;5.33)	1.07 (0.67;1.63)		
Q1, Q3 (IQR)	2.8 4.3 (1.5)	2.35 4.58 (2.23)	0.81 1.35 (0.54)		

SM17_01 Analysis of primary endpoint Ratio, SAS program: Primary_endpoint_pairwise_extra_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 14.3-13 *Ratio of extracted dose of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Wintergreen 3 mg - 60 min*

Statistics	ZS360	SW360	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.7408
Mean (Std)	1.58 (0.51)	1.58 (0.46)	1.02 (0.28)	Signed Rank	0.8317
Median (min;max)	1.61 (0.79;2.36)	1.48 (0.93;2.41)	1.03 (0.58;1.66)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.28 1.89 (0.61)	0.83 1.23 (0.4)		

SM17_01 Analysis of primary endpoint Ratio, SAS program: Primary_endpoint_pairwise_extra_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 14.3-14 *Ratio of extracted dose of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Peppermint 3 mg - 60 min*

Statistics	ZS360	ZP360	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.2829
Mean (Std)	1.58 (0.51)	1.53 (0.52)	1.08 (0.31)	Signed Rank	0.3247
Median (min;max)	1.61 (0.79;2.36)	1.51 (0.53;2.31)	1.03 (0.59;1.8)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.16 1.87 (0.71)	0.94 1.26 (0.32)		

SM17_01 Analysis of primary endpoint Ratio, SAS program: Primary_endpoint_pairwise_extra_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 14.3-15 *Ratio of extracted dose of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Spearmint 3 mg - 60 min*

Statistics	ZS360	ZSP360	Ratio between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.7991
Mean (Std)	1.58 (0.51)	1.63 (0.54)	1.02 (0.35)	Signed Rank	0.9323
Median (min;max)	1.61 (0.79;2.36)	1.44 (0.88;2.85)	0.97 (0.48;1.83)		
Q1, Q3 (IQR)	1.14 1.95 (0.81)	1.24 1.96 (0.72)	0.8 1.27 (0.47)		

SM17_01 Analysis of primary endpoint Ratio, SAS program: Primary_endpoint_pairwise_extra_ratio.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-11-16T07:50:22

Table 14.3-16 Difference in rate of extraction (%) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min

Statistics	ZS315	ZS3A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.5912
Mean (Std)	13.12 (5.06)	14.5 (11.05)	-1.38 (10.71)	Signed Rank	0.4423
Median (min;max)	12.65 (5.87;23.11)	12.1 (4.7;56.52)	0.85 (-41.51;6.87)		
Q1, Q3 (IQR)	9.07 17.12 (8.05)	10.51 14.36 (3.85)	-1.29 3.33 (4.62)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 14.3-17 Difference in rate of extraction (%) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min

Statistics	ZS360	ZS3A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.6282
Mean (Std)	52.14 (17.12)	50.57 (20.37)	1.57 (13.48)	Signed Rank	0.7019
Median (min;max)	52.57 (26.14;79.52)	46.32 (22.62;98.15)	1.2 (-21.84;27.41)		
Q1, Q3 (IQR)	37.19 64.65 (27.46)	38.44 65.95 (27.51)	-5.94 12.1 (18.04)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 14.3-18 Difference in rate of extraction (%) of nicotine (pairwise): ZYN[®] Smooth 6 mg - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min

Statistics	ZS615	ZS6A15	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.8500
Mean (Std)	17.06 (7.85)	17.33 (8.45)	-0.27 (5.92)	Signed Rank	0.8317
Median (min;max)	14.57 (7.85;39.44)	14.49 (8.96;36.96)	0.45 (-17.91;7.87)		
Q1, Q3 (IQR)	13.09 17.45 (4.36)	11.66 19.3 (7.64)	-1.96 3.96 (5.92)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 14.3-19 Difference in rate of extraction (%) of nicotine (pairwise): ZYN[®] Smooth 6 mg - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min

Statistics	ZS660	ZS6A60	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.1344
Mean (Std)	55.98 (18.08)	61.93 (23.66)	-5.96 (16.08)	Signed Rank	0.1964
Median (min;max)	53.4 (24.18;90.42)	62.9 (19.31;96.15)	-4.43 (-34.98;22.09)		
Q1, Q3 (IQR)	44.63 67.21 (22.58)	42.19 83.14 (40.95)	-20.2 4.87 (25.07)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 14.3-20 Difference in rate of extraction (%) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Wintergreen 3 mg - 60 min

Statistics	ZS360	SW360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.8946
Mean (Std)	52.14 (17.12)	51.69 (15.51)	0.45 (14.22)	Signed Rank	0.9323
Median (min;max)	52.57 (26.14;79.52)	48.26 (29.63;79.92)	1.72 (-25.81;30.46)		
Q1, Q3 (IQR)	37.19 64.65 (27.46)	42.08 62.57 (20.49)	-10.28 9.39 (19.67)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Table 14.3-21 Difference in rate of extraction (%) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Peppermint 3 mg - 60 min

Statistics	ZS360	ZP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.4186
Mean (Std)	52.14 (17.12)	49.49 (16.89)	2.66 (13.59)	Signed Rank	0.2837
Median (min;max)	52.57 (26.14;79.52)	47.99 (17.02;75.56)	2.76 (-23.19;34.34)		
Q1, Q3 (IQR)	37.19 64.65 (27.46)	38.43 60.77 (22.34)	-1.09 8.24 (9.33)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

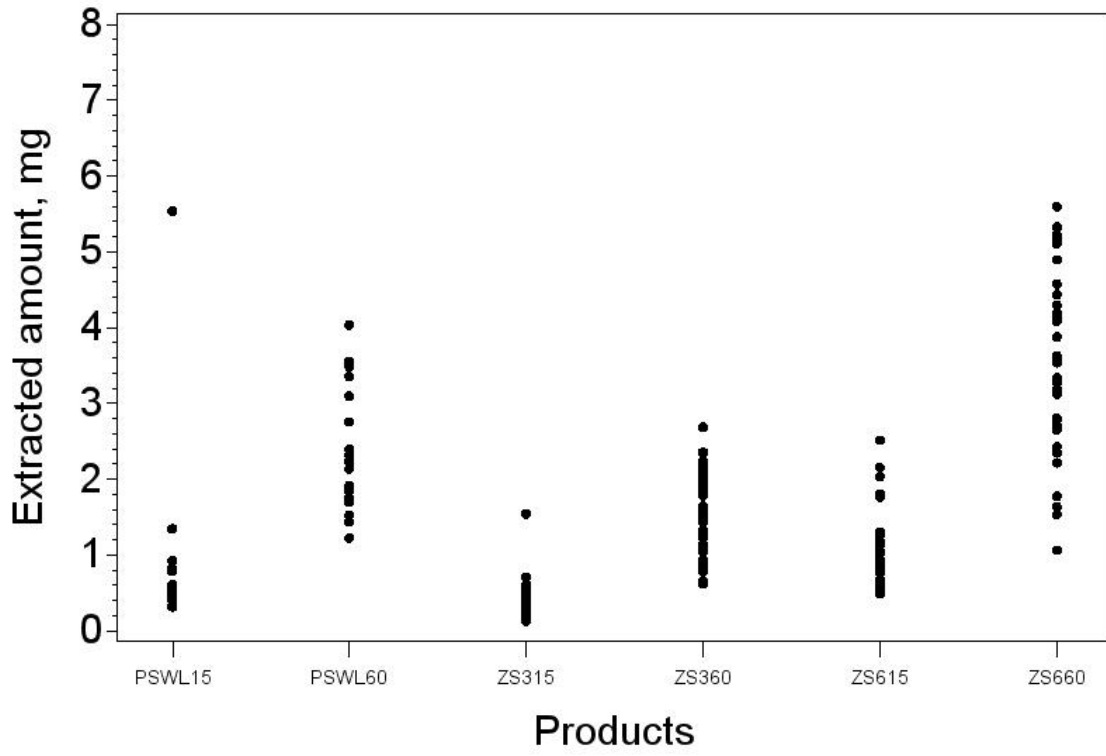
Table 14.3-22 Difference in rate of extraction (%) of nicotine (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Spearmint 3 mg - 60 min

Statistics	ZS360	ZSP360	Difference between products	Statistical test	P-value
n (nmiss)	18 (0)	18 (0)	18 (0)	Student's t	0.9041
Mean (Std)	52.14 (17.12)	52.64 (17.51)	-0.49 (17.13)	Signed Rank	0.7337
Median (min;max)	52.57 (26.14;79.52)	46.53 (28.57;91.98)	-0.99 (-28.85;34.56)		
Q1, Q3 (IQR)	37.19 64.65 (27.46)	40.29 63.17 (22.88)	-12.46 10.56 (23.02)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-07T10:27:50

Figure 14.3-1 Individual amount extracted nicotine for the respective product

Extracted amount nicotine divided by product



14.3.2 Secondary endpoints

Table 14.3-23 Summary statistics of pulse rate by treatment

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
Pulse Rate (beats/min)	Measured value	Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	Timepoint 0:00	18	59	94	71.9	70.5	10.7
			Timepoint 0:05	18	59	104	76.2	72.5	14
			Timepoint 0:10	18	61	105	79.6	78.5	11.2
			Timepoint 0:15	18	65	105	80.7	81	10.1
			Timepoint 0:30	18	55	99	73.2	71.5	11.4
			Timepoint 1:00	18	59	98	70.9	70.5	11
		Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	Timepoint 0:00	18	44	93	69.5	66.5	12.1
			Timepoint 0:05	18	55	88	73.7	74	7.65
			Timepoint 0:10	18	60	102	79.8	80	10.1
			Timepoint 0:15	18	62	102	77.7	75.5	11
			Timepoint 0:30	18	66	95	77.9	75.5	8.82
			Timepoint 1:00	18	65	94	77.3	76	8.69
		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	53	89	71.5	75	11.2
			Timepoint 0:05	18	58	86	70.7	70.5	8.91
			Timepoint 0:10	18	57	91	72.8	71.5	9.61
			Timepoint 0:15	18	58	94	74.3	74.5	11.3
			Timepoint 0:30	18	59	92	73.9	75.5	11.2
			Timepoint 1:00	18	56	91	75.1	75	10.1
		ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	54	98	70.8	70.5	11.6
			Timepoint 0:05	18	44	90	68.8	68	12.3
			Timepoint 0:10	18	59	94	72.8	72	10.4
			Timepoint 0:15	18	60	99	76.7	78.5	9.94
			Timepoint 0:30	18	50	82	67.4	65	7.94
			Timepoint 1:00	18	53	93	67.3	64.5	10.5

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	46	87	70.1	69.5	11.1
			Timepoint 0:05	18	48	94	69.4	68.5	13.3
			Timepoint 0:10	18	60	101	73.9	71.5	12.5
			Timepoint 0:15	18	60	99	74.3	72.5	10.1
			Timepoint 0:30	18	57	102	74.9	74	11.3
			Timepoint 1:00	18	58	94	75.7	77	9.41
		ZYN® Smooth 3 mg - 15 min	Timepoint 0:00	18	57	89	71.6	72.5	8.25
			Timepoint 0:05	18	56	89	74.2	74.5	9.18
			Timepoint 0:10	18	58	96	76.9	75	9.64
			Timepoint 0:15	18	59	102	78.7	80	9.58
			Timepoint 0:30	18	55	92	71.7	70.5	8.37
			Timepoint 1:00	18	52	100	68.8	65.5	12.5
		ZYN® Smooth 3 mg - 60 min	Timepoint 0:00	18	56	90	68.9	66.5	10
			Timepoint 0:05	18	50	88	68.9	66	11.8
			Timepoint 0:10	18	60	94	72.4	72	9.9
			Timepoint 0:15	18	62	98	74.9	70	12.3
			Timepoint 0:30	18	63	97	76.3	73.5	10.2
			Timepoint 1:00	18	58	115	75.7	73	13.1
		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	50	110	70.2	67.5	13.8
			Timepoint 0:05	18	59	95	71.7	71	11.5
			Timepoint 0:10	18	54	102	76.6	75	13.5
			Timepoint 0:15	18	62	113	78.2	78.5	12.4
			Timepoint 0:30	18	55	105	71.8	73.5	11.6
			Timepoint 1:00	18	53	96	66.8	66.5	9.96
		ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	58	84	68.2	66.5	8.88
			Timepoint 0:05	18	61	87	72.7	71.5	9.18
			Timepoint 0:10	18	62	98	79.3	77.5	11.6

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
			Timepoint 0:15	18	56	99	76.8	74	11.4
			Timepoint 0:30	18	61	113	79.2	76	13.6
			Timepoint 1:00	18	59	106	77.2	76.5	11.8
		ZYN® Smooth 6 mg - 15 min	Timepoint 0:00	18	55	86	70.4	69.5	8.97
			Timepoint 0:05	18	57	102	71.8	70.5	13.1
			Timepoint 0:10	18	60	111	76.5	75	12.4
			Timepoint 0:15	18	63	125	81.8	79	14.3
			Timepoint 0:30	18	58	95	73.2	70.5	9.72
			Timepoint 1:00	18	56	97	69.7	66.5	10.2
		ZYN® Smooth 6 mg - 60 min	Timepoint 0:00	18	47	91	67.6	68	9.43
			Timepoint 0:05	18	49	86	68.7	68	9.23
			Timepoint 0:10	18	57	98	76.3	77	10.1
			Timepoint 0:15	18	56	96	74.9	75	9.6
			Timepoint 0:30	18	58	94	75.7	75	9.68
			Timepoint 1:00	18	59	110	76.2	75	11.3
		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	54	90	71.1	69.5	12.3
			Timepoint 0:05	18	52	100	73.9	74.5	14.2
			Timepoint 0:10	18	59	98	73.8	75	10.4
			Timepoint 0:15	18	60	100	74.4	73.5	10.9
			Timepoint 0:30	18	61	107	75.7	73	11.5
			Timepoint 1:00	18	60	110	78.6	73.5	13.1
		ZYN® Wintergreen 3 mg (Flavor) - 60 min	Timepoint 0:00	18	56	95	71.1	68.5	11.5
			Timepoint 0:05	18	56	90	70.8	68.5	10
			Timepoint 0:10	18	58	94	73.9	71	12.1
			Timepoint 0:15	18	62	98	74.6	70	11
			Timepoint 0:30	18	59	107	75.1	72.5	13.2
			Timepoint 1:00	18	59	117	76.9	75.5	13.7

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	Timepoint 0:00	18	55	87	68.6	67	9.2
			Timepoint 0:05	18	53	91	70	71	11.6
			Timepoint 0:10	18	56	105	74.3	73	12.2
			Timepoint 0:15	18	62	108	74.4	71	11.4
			Timepoint 0:30	18	61	97	73.3	73	9.31
			Timepoint 1:00	18	55	116	74.7	75	13.1
	Absolute change from pre-dose baseline	Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-7	22	4.33	2	7.46
			Timepoint 0:10	18	-2	25	7.72	7.5	6.96
			Timepoint 0:15	18	-3	24	8.78	7	7.86
			Timepoint 0:30	18	-6	24	1.33	0	6.67
			Timepoint 1:00	18	-19	14	-0.944	-1.5	8.36
		Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-13	30	4.22	5	9.32
			Timepoint 0:10	18	-12	35	10.3	9	9.6
			Timepoint 0:15	18	-17	21	8.22	6.5	8.67
			Timepoint 0:30	18	-19	30	8.44	8.5	11
			Timepoint 1:00	18	-22	27	7.83	7	11.2
		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-12	8	-0.778	0	5.98
			Timepoint 0:10	18	-11	9	1.28	2	5.76
			Timepoint 0:15	18	-9	11	2.83	4	5
			Timepoint 0:30	18	-9	14	2.44	1.5	6.11
			Timepoint 1:00	18	-19	29	3.56	3	11
		ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-22	12	-2	1	9.23
			Timepoint 0:10	18	-12	16	2	2	7

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
			Timepoint 0:15	18	-16	25	5.83	5	9.7
			Timepoint 0:30	18	-20	10	-3.39	-3.5	7.24
			Timepoint 1:00	18	-25	8	-3.56	-3	8.69
		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-9	10	-0.722	-1	5.24
			Timepoint 0:10	18	-6	18	3.78	1.5	7.3
			Timepoint 0:15	18	-9	27	4.22	3	8.54
			Timepoint 0:30	18	-5	40	4.83	2.5	10.9
			Timepoint 1:00	18	-6	22	5.61	2.5	8.95
		ZYN® Smooth 3 mg - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-8	16	2.56	3	6.26
			Timepoint 0:10	18	-7	19	5.33	6	6.32
			Timepoint 0:15	18	-9	22	7.11	7	7.05
			Timepoint 0:30	18	-18	10	0.0556	1	6.33
			Timepoint 1:00	18	-28	18	-2.83	-3.5	9.74
		ZYN® Smooth 3 mg - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-12	16	-0.0556	0	6.41
			Timepoint 0:10	18	-10	21	3.5	2.5	7.55
			Timepoint 0:15	18	-7	29	6	3.5	8.74
			Timepoint 0:30	18	-4	28	7.33	5.5	8.46
			Timepoint 1:00	18	-5	25	6.78	5	9.69
		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-15	24	1.44	0.5	8.19
			Timepoint 0:10	18	-11	28	6.39	5	9.84
			Timepoint 0:15	18	-19	24	7.94	9.5	10.4
			Timepoint 0:30	18	-8	14	1.56	1.5	6.28
			Timepoint 1:00	18	-17	14	-3.44	-2.5	7.78

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-10	17	4.44	4	6.61
			Timepoint 0:10	18	-6	34	11.1	11	9.55
			Timepoint 0:15	18	-6	23	8.61	8	8.91
			Timepoint 0:30	18	-12	40	11	10	13.7
			Timepoint 1:00	18	-8	37	9	7	11.6
		ZYN® Smooth 6 mg - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-8	16	1.33	0	6.82
			Timepoint 0:10	18	-5	25	6.06	5.5	7.06
			Timepoint 0:15	18	-1	39	11.4	10	9.46
			Timepoint 0:30	18	-7	17	2.72	1.5	5.74
			Timepoint 1:00	18	-18	11	-0.778	-1.5	7.34
		ZYN® Smooth 6 mg - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-12	13	1.11	0	6.79
			Timepoint 0:10	18	-6	23	8.72	9	7.45
			Timepoint 0:15	18	-3	19	7.28	6.5	6.33
			Timepoint 0:30	18	-5	21	8.06	6.5	7.33
			Timepoint 1:00	18	-1	22	8.61	6	7.59
		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-9	36	2.83	1	9.67
			Timepoint 0:10	18	-11	15	2.78	1.5	7.07
			Timepoint 0:15	18	-13	15	3.33	4.5	8.07
			Timepoint 0:30	18	-14	20	4.67	5	9.53
			Timepoint 1:00	18	-13	42	7.56	8	12.2
		ZYN® Wintergreen 3 mg (Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-11	7	-0.222	0.5	3.96
			Timepoint 0:10	18	-8	18	2.89	0.5	6.3

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
			Timepoint 0:15	18	-9	17	3.5	3	7.1
			Timepoint 0:30	18	-10	16	4	5	7.05
			Timepoint 1:00	18	-29	29	5.89	6	13
		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-6	11	1.39	1	4.46
			Timepoint 0:10	18	-4	18	5.67	5	5.55
			Timepoint 0:15	18	-6	21	5.78	6	6
			Timepoint 0:30	18	-1	13	4.72	3	4.75
			Timepoint 1:00	18	-2	30	6.11	3.5	9.15
	Relative change from pre-dose baseline (%)	Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-10	31	5.94	2.5	10.5
			Timepoint 0:10	18	-3	42	11.3	11.5	11.1
			Timepoint 0:15	18	-4	41	13.3	10.5	12.6
			Timepoint 0:30	18	-10	38	2.17	0	10.3
			Timepoint 1:00	18	-21	20	-0.833	-2.5	11.3
		Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-14	68	8.28	8	17.5
			Timepoint 0:10	18	-13	80	16.8	13	18.7
			Timepoint 0:15	18	-18	48	13.2	10.5	13.4
			Timepoint 0:30	18	-20	68	14.7	12.5	18.8
			Timepoint 1:00	18	-24	48	13.6	9.5	17.4
		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-16	15	-0.222	0	8.52
			Timepoint 0:10	18	-13	17	2.56	2.5	8.79
			Timepoint 0:15	18	-13	16	4.28	5.5	7.45
			Timepoint 0:30	18	-12	18	3.89	2	8.74
			Timepoint 1:00	18	-22	51	6.5	4.5	17.1

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-29	16	-2.33	1	12.7
			Timepoint 0:10	18	-14	21	3.56	3	9.61
			Timepoint 0:15	18	-19	46	9.78	8	15.5
			Timepoint 0:30	18	-24	19	-3.72	-4.5	9.57
			Timepoint 1:00	18	-30	13	-4.11	-4	11.5
		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-13	15	-1.28	-1.5	7.32
			Timepoint 0:10	18	-8	35	5.94	2.5	11.4
			Timepoint 0:15	18	-11	59	7.44	4.5	15.5
			Timepoint 0:30	18	-7	87	8.78	4	21.5
			Timepoint 1:00	18	-9	39	9.56	3.5	15.7
		ZYN® Smooth 3 mg - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-10	22	3.78	4	8.74
			Timepoint 0:10	18	-8	25	7.72	8	8.57
			Timepoint 0:15	18	-10	28	10.3	9	9.51
			Timepoint 0:30	18	-23	13	0.278	1	8.32
			Timepoint 1:00	18	-35	22	-4	-5	12.3
		ZYN® Smooth 3 mg - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-16	25	-0.0556	0	9.46
			Timepoint 0:10	18	-12	29	5.67	3.5	10.9
			Timepoint 0:15	18	-9	45	9.06	5	13.2
			Timepoint 0:30	18	-5	43	11.6	8	13.6
			Timepoint 1:00	18	-7	39	10.3	8.5	14
		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-14	35	3.17	1	11.5
			Timepoint 0:10	18	-14	41	10.2	8.5	14.3

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
			Timepoint 0:15	18	-23	41	13.1	13.5	16.2
			Timepoint 0:30	18	-10	21	3.06	2.5	8.81
			Timepoint 1:00	18	-21	28	-3.61	-3.5	11.3
		ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-13	29	6.89	5	9.85
			Timepoint 0:10	18	-8	59	16.9	14.5	15.5
			Timepoint 0:15	18	-8	38	13.1	12	13.5
			Timepoint 0:30	18	-16	69	17.2	16	21
			Timepoint 1:00	18	-10	62	14.3	10.5	18.6
		ZYN® Smooth 6 mg - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-12	19	1.61	0	9.05
			Timepoint 0:10	18	-6	29	8.56	8	9.03
			Timepoint 0:15	18	-1	45	16.1	14	12.3
			Timepoint 0:30	18	-9	26	4.06	2	8.43
			Timepoint 1:00	18	-21	15	-0.778	-2.5	10.1
		ZYN® Smooth 6 mg - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-17	18	2.28	0	9.9
			Timepoint 0:10	18	-8	34	13.6	14	11.8
			Timepoint 0:15	18	-4	30	11.3	9	10
			Timepoint 0:30	18	-7	34	12.7	9.5	12
			Timepoint 1:00	18	-1	42	13.3	8.5	12.4
		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-11	56	4.44	1.5	14.8
			Timepoint 0:10	18	-13	22	5	2.5	10.1
			Timepoint 0:15	18	-15	22	5.72	7.5	10.7
			Timepoint 0:30	18	-16	37	7.83	7	13.8
			Timepoint 1:00	18	-15	62	12.2	10.5	18.4

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Wintergreen 3 mg (Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-12	13	0.111	0.5	5.55
			Timepoint 0:10	18	-8	24	4.33	1	8.83
			Timepoint 0:15	18	-9	29	5.67	4.5	10.3
			Timepoint 0:30	18	-11	24	5.78	7.5	9.62
			Timepoint 1:00	18	-31	33	9.5	9.5	16.7
		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	-10	17	1.72	2	6.54
			Timepoint 0:10	18	-7	23	8.17	7.5	7.68
			Timepoint 0:15	18	-8	24	8.5	9	8.47
			Timepoint 0:30	18	-1	23	7.44	4.5	7.54
			Timepoint 1:00	18	-3	54	9.17	4.5	14

SM17_01 VS tabulations, SAS program: safety_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:36:14

Table 14.3-24 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN® Smooth 3 mg - 15 min

Time point (min)	Statistics	PSWL15	ZS315	Change in PSWL15	Change in ZS315	Change in PSWL15 - Change in ZS315	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	71.89 (10.71)	71.61 (8.25)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	70.5 (59;94)	72.5 (57;89)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	64 78 (14)	67 77 (10)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3562
	Mean (Std)	76.22 (13.97)	74.17 (9.18)	4.33 (7.46)	2.56 (6.26)	1.78 (7.95)	Signed Rank	0.3634
	Median (min;max)	72.5 (59;104)	74.5 (56;89)	2 (-7;22)	3 (-8;16)	1.5 (-14;14)		
	Q1, Q3 (IQR)	65 90 (25)	67 81 (14)	0 8 (8)	-1 7 (8)	-4 9 (13)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1633
	Mean (Std)	79.61 (11.22)	76.94 (9.64)	7.72 (6.96)	5.33 (6.32)	2.39 (6.95)	Signed Rank	0.2408
	Median (min;max)	78.5 (61;105)	75 (58;96)	7.5 (-2;25)	6 (-7;19)	3 (-8;16)		
	Q1, Q3 (IQR)	73 88 (15)	71 83 (12)	2 12 (10)	0 10 (10)	-3 5 (8)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3685
	Mean (Std)	80.67 (10.06)	78.72 (9.58)	8.78 (7.86)	7.11 (7.05)	1.67 (7.65)	Signed Rank	0.4371
	Median (min;max)	81 (65;105)	80 (59;102)	7 (-3;24)	7 (-9;22)	2 (-10;16)		
	Q1, Q3 (IQR)	72 88 (16)	74 81 (7)	4 12 (8)	4 14 (10)	-4 9 (13)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5744
	Mean (Std)	73.22 (11.44)	71.67 (8.37)	1.33 (6.67)	0.06 (6.33)	1.28 (9.47)	Signed Rank	0.8907
	Median (min;max)	71.5 (55;99)	70.5 (55;92)	0 (-6;24)	1 (-18;10)	-0.5 (-10;27)		
	Q1, Q3 (IQR)	64 79 (15)	67 76 (9)	-2 3 (5)	-2 4 (6)	-5 1 (6)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5448
	Mean (Std)	70.94 (10.96)	68.78 (12.51)	-0.94 (8.36)	-2.83 (9.74)	1.89 (12.97)	Signed Rank	0.4686
	Median (min;max)	70.5 (59;98)	65.5 (52;100)	-1.5 (-19;14)	-3.5 (-28;18)	2.5 (-29;29)		
	Q1, Q3 (IQR)	61 74 (13)	63 71 (8)	-6 6 (12)	-7 0 (7)	-7 8 (15)		

SM17 01 Analysis of secondary endpoint - Pulse, SAS program: sec endpoint pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:15:52

Table 14.3-25 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 6 mg - 15 min

Time point (min)	Statistics	PSWL15	ZS615	Change in PSWL15	Change in ZS615	Change in PSWL15 - Change in ZS615	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	71.89 (10.71)	70.44 (8.97)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	70.5 (59;94)	69.5 (55;86)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	64 78 (14)	64 77 (13)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1330
	Mean (Std)	76.22 (13.97)	71.78 (13.09)	4.33 (7.46)	1.33 (6.82)	3 (8.07)	Signed Rank	0.1408
	Median (min;max)	72.5 (59;104)	70.5 (57;102)	2 (-7;22)	0 (-8;16)	5 (-8;19)		
	Q1, Q3 (IQR)	65 90 (25)	60 75 (15)	0 8 (8)	-4 6 (10)	-5 8 (13)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4327
	Mean (Std)	79.61 (11.22)	76.5 (12.42)	7.72 (6.96)	6.06 (7.06)	1.67 (8.8)	Signed Rank	0.4873
	Median (min;max)	78.5 (61;105)	75 (60;111)	7.5 (-2;25)	5.5 (-5;25)	2.5 (-14;24)		
	Q1, Q3 (IQR)	73 88 (15)	68 80 (12)	2 12 (10)	2 10 (8)	-4 7 (11)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2427
	Mean (Std)	80.67 (10.06)	81.83 (14.34)	8.78 (7.86)	11.39 (9.46)	-2.61 (9.15)	Signed Rank	0.3390
	Median (min;max)	81 (65;105)	79 (63;125)	7 (-3;24)	10 (-1;39)	-3 (-28;9)		
	Q1, Q3 (IQR)	72 88 (16)	72 91 (19)	4 12 (8)	6 13 (7)	-7 4 (11)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4887
	Mean (Std)	73.22 (11.44)	73.17 (9.72)	1.33 (6.67)	2.72 (5.74)	-1.39 (8.33)	Signed Rank	0.2583
	Median (min;max)	71.5 (55;99)	70.5 (58;95)	0 (-6;24)	1.5 (-7;17)	-3 (-21;19)		
	Q1, Q3 (IQR)	64 79 (15)	68 82 (14)	-2 3 (5)	-1 6 (7)	-5 3 (8)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9277
	Mean (Std)	70.94 (10.96)	69.67 (10.21)	-0.94 (8.36)	-0.78 (7.34)	-0.17 (7.68)	Signed Rank	0.9745
	Median (min;max)	70.5 (59;98)	66.5 (56;97)	-1.5 (-19;14)	-1.5 (-18;11)	0.5 (-18;16)		
	Q1, Q3 (IQR)	61 74 (13)	65 74 (9)	-6 6 (12)	-4 4 (8)	-5 4 (9)		

SM17 01 Analysis of secondary endpoint - Pulse, SAS program: sec endpoint pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:15:52

Table 14.3-26 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	Change in PSWL15	ZS3A15	Change in PSWL15	ZS3A15	Change in PSWL15 - ZS3A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	71.89 (10.71)	70.83 (11.65)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	70.5 (59;94)	70.5 (54;98)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	64 78 (14)	62 76 (14)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0505
	Mean (Std)	76.22 (13.97)	68.83 (12.33)	4.33 (7.46)	-2 (9.23)	6.33 (12.77)	Signed Rank	0.1108
	Median (min;max)	72.5 (59;104)	68 (44;90)	2 (-7;22)	1 (-22;12)	1 (-8;40)		
	Q1, Q3 (IQR)	65 90 (25)	62 78 (16)	0 8 (8)	-8 4 (12)	-1 11 (12)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0191
	Mean (Std)	79.61 (11.22)	72.83 (10.38)	7.72 (6.96)	2 (7)	5.72 (9.37)	Signed Rank	0.0261
	Median (min;max)	78.5 (61;105)	72 (59;94)	7.5 (-2;25)	2 (-12;16)	4 (-8;25)		
	Q1, Q3 (IQR)	73 88 (15)	66 79 (13)	2 12 (10)	-4 5 (9)	-2 10 (12)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1812
	Mean (Std)	80.67 (10.06)	76.67 (9.94)	8.78 (7.86)	5.83 (9.7)	2.94 (8.96)	Signed Rank	0.2158
	Median (min;max)	81 (65;105)	78.5 (60;99)	7 (-3;24)	5 (-16;25)	5 (-11;26)		
	Q1, Q3 (IQR)	72 88 (16)	68 81 (13)	4 12 (8)	1 13 (12)	-3 7 (10)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0494
	Mean (Std)	73.22 (11.44)	67.44 (7.94)	1.33 (6.67)	-3.39 (7.24)	4.72 (9.47)	Signed Rank	0.0753
	Median (min;max)	71.5 (55;99)	65 (50;82)	0 (-6;24)	-3.5 (-20;10)	2.5 (-10;26)		
	Q1, Q3 (IQR)	64 79 (15)	64 72 (8)	-2 3 (5)	-5 1 (6)	-2 8 (10)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3547
	Mean (Std)	70.94 (10.96)	67.28 (10.53)	-0.94 (8.36)	-3.56 (8.69)	2.61 (11.64)	Signed Rank	0.7095
	Median (min;max)	70.5 (59;98)	64.5 (53;93)	-1.5 (-19;14)	-3 (-25;8)	0 (-13;24)		
	Q1, Q3 (IQR)	61 74 (13)	61 69 (8)	-6 6 (12)	-8 4 (12)	-7 12 (19)		

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Table 14.3-27 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	PSWL15	ZS6A15	Change in PSWL15	Change in ZS6A15	Change in PSWL15 - Change in ZS6A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	71.89 (10.71)	70.22 (13.81)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	70.5 (59;94)	67.5 (50;110)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	64 78 (14)	62 77 (15)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3485
	Mean (Std)	76.22 (13.97)	71.67 (11.46)	4.33 (7.46)	1.44 (8.19)	2.89 (12.71)	Signed Rank	0.2576
	Median (min;max)	72.5 (59;104)	71 (59;95)	2 (-7;22)	0.5 (-15;24)	1 (-23;25)		
	Q1, Q3 (IQR)	65 90 (25)	61 75 (14)	0 8 (8)	-2 5 (7)	-1 7 (8)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5980
	Mean (Std)	79.61 (11.22)	76.61 (13.45)	7.72 (6.96)	6.39 (9.84)	1.33 (10.53)	Signed Rank	0.7018
	Median (min;max)	78.5 (61;105)	75 (54;102)	7.5 (-2;25)	5 (-11;28)	0.5 (-25;21)		
	Q1, Q3 (IQR)	73 88 (15)	66 85 (19)	2 12 (10)	1 11 (10)	-4 6 (10)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7862
	Mean (Std)	80.67 (10.06)	78.17 (12.38)	8.78 (7.86)	7.94 (10.37)	0.83 (12.83)	Signed Rank	0.9701
	Median (min;max)	81 (65;105)	78.5 (62;113)	7 (-3;24)	9.5 (-19;24)	0 (-20;29)		
	Q1, Q3 (IQR)	72 88 (16)	66 84 (18)	4 12 (8)	2 13 (11)	-9 8 (17)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9251
	Mean (Std)	73.22 (11.44)	71.78 (11.62)	1.33 (6.67)	1.56 (6.28)	-0.22 (9.88)	Signed Rank	0.4736
	Median (min;max)	71.5 (55;99)	73.5 (55;105)	0 (-6;24)	1.5 (-8;14)	-4.5 (-9;31)		
	Q1, Q3 (IQR)	64 79 (15)	64 78 (14)	-2 3 (5)	-3 6 (9)	-7 4 (11)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3991
	Mean (Std)	70.94 (10.96)	66.78 (9.96)	-0.94 (8.36)	-3.44 (7.78)	2.5 (12.26)	Signed Rank	0.4456
	Median (min;max)	70.5 (59;98)	66.5 (53;96)	-1.5 (-19;14)	-2.5 (-17;14)	3 (-25;24)		
	Q1, Q3 (IQR)	61 74 (13)	60 71 (11)	-6 6 (12)	-9 0 (9)	-6 15 (21)		

SM17 01 Analysis of secondary endpoint - Pulse, SAS program: sec endpoint pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:15:52

Table 14.3-28 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 3 mg - 60 min

Time point (min)	Statistics	PSWL60	ZS360	Change in PSWL60	Change in ZS360	Change in PSWL60 - Change in ZS360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	68.94 (10.04)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	66.5 (56;90)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	62 74 (12)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1025
	Mean (Std)	73.72 (7.65)	68.89 (11.79)	4.22 (9.32)	-0.06 (6.41)	4.28 (10.52)	Signed Rank	0.0549
	Median (min;max)	74 (55;88)	66 (50;88)	5 (-13;30)	0 (-12;16)	6 (-24;22)		
	Q1, Q3 (IQR)	70 80 (10)	59 80 (21)	0 8 (8)	-3 2 (5)	0 9 (9)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0350
	Mean (Std)	79.78 (10.06)	72.44 (9.9)	10.28 (9.6)	3.5 (7.55)	6.78 (12.55)	Signed Rank	0.0053
	Median (min;max)	80 (60;102)	72 (60;94)	9 (-12;35)	2.5 (-10;21)	7.5 (-33;21)		
	Q1, Q3 (IQR)	72 85 (13)	63 79 (16)	5 13 (8)	1 6 (5)	2 16 (14)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4426
	Mean (Std)	77.72 (10.99)	74.94 (12.33)	8.22 (8.67)	6 (8.74)	2.22 (11.99)	Signed Rank	0.1065
	Median (min;max)	75.5 (62;102)	70 (62;98)	6.5 (-17;21)	3.5 (-7;29)	3 (-36;19)		
	Q1, Q3 (IQR)	70 85 (15)	64 87 (23)	5 14 (9)	1 9 (8)	-1 9 (10)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7213
	Mean (Std)	77.94 (8.82)	76.28 (10.24)	8.44 (11.02)	7.33 (8.46)	1.11 (13)	Signed Rank	0.3299
	Median (min;max)	75.5 (66;95)	73.5 (63;97)	8.5 (-19;30)	5.5 (-4;28)	4 (-37;16)		
	Q1, Q3 (IQR)	72 84 (12)	69 83 (14)	3 16 (13)	3 8 (5)	-5 9 (14)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7539
	Mean (Std)	77.33 (8.69)	75.72 (13.11)	7.83 (11.19)	6.78 (9.69)	1.06 (14.06)	Signed Rank	0.4351
	Median (min;max)	76 (65;94)	73 (58;115)	7 (-22;27)	5 (-5;25)	5.5 (-39;16)		
	Q1, Q3 (IQR)	71 83 (12)	68 82 (14)	3 18 (15)	-3 16 (19)	-7 11 (18)		

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Table 14.3-29 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Smooth 6 mg - 60 min

Time point (min)	Statistics	PSWL60	ZS660	Change in PSWL60	Change in ZS660	Change in PSWL60 - Change in ZS660	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	67.61 (9.43)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	68 (47;91)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	64 72 (8)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3280
	Mean (Std)	73.72 (7.65)	68.72 (9.23)	4.22 (9.32)	1.11 (6.79)	3.11 (13.11)	Signed Rank	0.3234
	Median (min;max)	74 (55;88)	68 (49;86)	5 (-13;30)	0 (-12;13)	3.5 (-18;42)		
	Q1, Q3 (IQR)	70 80 (10)	63 74 (11)	0 8 (8)	-3 6 (9)	-3 9 (12)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5315
	Mean (Std)	79.78 (10.06)	76.33 (10.12)	10.28 (9.6)	8.72 (7.45)	1.56 (10.33)	Signed Rank	0.5012
	Median (min;max)	80 (60;102)	77 (57;98)	9 (-12;35)	9 (-6;23)	2 (-21;21)		
	Q1, Q3 (IQR)	72 85 (13)	68 84 (16)	5 13 (8)	6 14 (8)	-4 9 (13)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.6915
	Mean (Std)	77.72 (10.99)	74.89 (9.6)	8.22 (8.67)	7.28 (6.33)	0.94 (9.93)	Signed Rank	0.5294
	Median (min;max)	75.5 (62;102)	75 (56;96)	6.5 (-17;21)	6.5 (-3;19)	1.5 (-22;24)		
	Q1, Q3 (IQR)	70 85 (15)	68 81 (13)	5 14 (9)	3 11 (8)	-4 5 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8483
	Mean (Std)	77.94 (8.82)	75.67 (9.68)	8.44 (11.02)	8.06 (7.33)	0.39 (8.49)	Signed Rank	0.8060
	Median (min;max)	75.5 (66;95)	75 (58;94)	8.5 (-19;30)	6.5 (-5;21)	1.5 (-18;15)		
	Q1, Q3 (IQR)	72 84 (12)	69 84 (15)	3 16 (13)	3 14 (11)	-4 7 (11)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7665
	Mean (Std)	77.33 (8.69)	76.22 (11.31)	7.83 (11.19)	8.61 (7.59)	-0.78 (10.94)	Signed Rank	0.7904
	Median (min;max)	76 (65;94)	75 (59;110)	7 (-22;27)	6 (-1;22)	-1 (-22;18)		
	Q1, Q3 (IQR)	71 83 (12)	71 78 (7)	3 18 (15)	3 15 (12)	-10 6 (16)		

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Table 14.3-30 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	PSWL60	ZS3A60	Change in PSWL60	Change in ZS3A60	Change in PSWL60 - Change in ZS3A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	70.11 (11.1)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	69.5 (46;87)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	64 80 (16)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0564
	Mean (Std)	73.72 (7.65)	69.39 (13.27)	4.22 (9.32)	-0.72 (5.24)	4.94 (10.25)	Signed Rank	0.0582
	Median (min;max)	74 (55;88)	68.5 (48;94)	5 (-13;30)	-1 (-9;10)	6 (-15;28)		
	Q1, Q3 (IQR)	70 80 (10)	60 76 (16)	0 8 (8)	-5 2 (7)	0 9 (9)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0098
	Mean (Std)	79.78 (10.06)	73.89 (12.47)	10.28 (9.6)	3.78 (7.3)	6.5 (9.49)	Signed Rank	0.0064
	Median (min;max)	80 (60;102)	71.5 (60;101)	9 (-12;35)	1.5 (-6;18)	6 (-20;22)		
	Q1, Q3 (IQR)	72 85 (13)	64 81 (17)	5 13 (8)	-2 8 (10)	4 12 (8)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0587
	Mean (Std)	77.72 (10.99)	74.33 (10.1)	8.22 (8.67)	4.22 (8.54)	4 (8.37)	Signed Rank	0.0225
	Median (min;max)	75.5 (62;102)	72.5 (60;99)	6.5 (-17;21)	3 (-9;27)	4.5 (-21;19)		
	Q1, Q3 (IQR)	70 85 (15)	70 77 (7)	5 14 (9)	1 7 (6)	2 8 (6)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1381
	Mean (Std)	77.94 (8.82)	74.94 (11.3)	8.44 (11.02)	4.83 (10.87)	3.61 (9.85)	Signed Rank	0.0913
	Median (min;max)	75.5 (66;95)	74 (57;102)	8.5 (-19;30)	2.5 (-5;40)	5 (-23;19)		
	Q1, Q3 (IQR)	72 84 (12)	67 83 (16)	3 16 (13)	-2 8 (10)	2 8 (6)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3350
	Mean (Std)	77.33 (8.69)	75.72 (9.41)	7.83 (11.19)	5.61 (8.95)	2.22 (9.5)	Signed Rank	0.1919
	Median (min;max)	76 (65;94)	77 (58;94)	7 (-22;27)	2.5 (-6;22)	3 (-24;16)		
	Q1, Q3 (IQR)	71 83 (12)	70 84 (14)	3 18 (15)	-1 12 (13)	-3 9 (12)		

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Table 14.3-31 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	PSWL60	ZS6A60	Change in PSWL60	Change in ZS6A60	Change in PSWL60 - Change in ZS6A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	68.22 (8.88)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	66.5 (58;84)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	60 76 (16)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9195
	Mean (Std)	73.72 (7.65)	72.67 (9.18)	4.22 (9.32)	4.44 (6.61)	-0.22 (9.19)	Signed Rank	0.6687
	Median (min;max)	74 (55;88)	71.5 (61;87)	5 (-13;30)	4 (-10;17)	-2 (-12;20)		
	Q1, Q3 (IQR)	70 80 (10)	65 81 (16)	0 8 (8)	2 7 (5)	-7 5 (12)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7489
	Mean (Std)	79.78 (10.06)	79.33 (11.63)	10.28 (9.6)	11.11 (9.55)	-0.83 (10.87)	Signed Rank	0.8992
	Median (min;max)	80 (60;102)	77.5 (62;98)	9 (-12;35)	11 (-6;34)	-0.5 (-23;19)		
	Q1, Q3 (IQR)	72 85 (13)	71 91 (20)	5 13 (8)	3 16 (13)	-8 5 (13)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8630
	Mean (Std)	77.72 (10.99)	76.83 (11.37)	8.22 (8.67)	8.61 (8.91)	-0.39 (9.42)	Signed Rank	0.9413
	Median (min;max)	75.5 (62;102)	74 (56;99)	6.5 (-17;21)	8 (-6;23)	-1 (-19;16)		
	Q1, Q3 (IQR)	70 85 (15)	70 86 (16)	5 14 (9)	3 16 (13)	-5 7 (12)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5214
	Mean (Std)	77.94 (8.82)	79.22 (13.61)	8.44 (11.02)	11 (13.73)	-2.56 (16.56)	Signed Rank	0.6032
	Median (min;max)	75.5 (66;95)	76 (61;113)	8.5 (-19;30)	10 (-12;40)	-1.5 (-35;23)		
	Q1, Q3 (IQR)	72 84 (12)	69 85 (16)	3 16 (13)	2 20 (18)	-16 12 (28)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7698
	Mean (Std)	77.33 (8.69)	77.22 (11.77)	7.83 (11.19)	9 (11.64)	-1.17 (16.64)	Signed Rank	0.7405
	Median (min;max)	76 (65;94)	76.5 (59;106)	7 (-22;27)	7 (-8;37)	-3 (-29;29)		
	Q1, Q3 (IQR)	71 83 (12)	69 83 (14)	3 18 (15)	1 14 (13)	-16 8 (24)		

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Table 14.3-32 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Wintergreen (nicotine) 3 mg - 60 min

Time point (min)	Statistics	PSWL60	SW360	Change in PSWL60	Change in SW360	Change in PSWL60 - Change in SW360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	68.61 (9.2)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	67 (55;87)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	60 75 (15)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3057
	Mean (Std)	73.72 (7.65)	70 (11.6)	4.22 (9.32)	1.39 (4.46)	2.83 (11.38)	Signed Rank	0.2781
	Median (min;max)	74 (55;88)	71 (53;91)	5 (-13;30)	1 (-6;11)	3.5 (-19;35)		
	Q1, Q3 (IQR)	70 80 (10)	61 78 (17)	0 8 (8)	-2 3 (5)	-1 7 (8)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0877
	Mean (Std)	79.78 (10.06)	74.28 (12.19)	10.28 (9.6)	5.67 (5.55)	4.61 (10.8)	Signed Rank	0.0426
	Median (min;max)	80 (60;102)	73 (56;105)	9 (-12;35)	5 (-4;18)	5.5 (-19;35)		
	Q1, Q3 (IQR)	72 85 (13)	67 80 (13)	5 13 (8)	1 8 (7)	-1 9 (10)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3140
	Mean (Std)	77.72 (10.99)	74.39 (11.35)	8.22 (8.67)	5.78 (6)	2.44 (10)	Signed Rank	0.2674
	Median (min;max)	75.5 (62;102)	71 (62;108)	6.5 (-17;21)	6 (-6;21)	1 (-21;27)		
	Q1, Q3 (IQR)	70 85 (15)	66 81 (15)	5 14 (9)	2 8 (6)	-3 10 (13)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2119
	Mean (Std)	77.94 (8.82)	73.33 (9.31)	8.44 (11.02)	4.72 (4.75)	3.72 (12.17)	Signed Rank	0.1629
	Median (min;max)	75.5 (66;95)	73 (61;97)	8.5 (-19;30)	3 (-1;13)	4 (-21;28)		
	Q1, Q3 (IQR)	72 84 (12)	66 77 (11)	3 16 (13)	1 10 (9)	-3 9 (12)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.6355
	Mean (Std)	77.33 (8.69)	74.72 (13.05)	7.83 (11.19)	6.11 (9.15)	1.72 (15.14)	Signed Rank	0.5087
	Median (min;max)	76 (65;94)	75 (55;116)	7 (-22;27)	3.5 (-2;30)	2 (-26;23)		
	Q1, Q3 (IQR)	71 83 (12)	66 79 (13)	3 18 (15)	1 6 (5)	-2 14 (16)		

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Table 14.3-33 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Wintergreen (flavor) 3 mg - 60 min

Time point (min)	Statistics	PSWL60	SW360F	Change in PSWL60	Change in SW360F	Change in PSWL60 - Change in SW360F	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	71.06 (11.49)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	68.5 (56;95)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	62 75 (13)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0712
	Mean (Std)	73.72 (7.65)	70.83 (10.05)	4.22 (9.32)	-0.22 (3.96)	4.44 (9.8)	Signed Rank	0.0801
	Median (min;max)	74 (55;88)	68.5 (56;90)	5 (-13;30)	0.5 (-11;7)	3.5 (-12;27)		
	Q1, Q3 (IQR)	70 80 (10)	62 77 (15)	0 8 (8)	-2 2 (4)	1 9 (8)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0013
	Mean (Std)	79.78 (10.06)	73.94 (12.09)	10.28 (9.6)	2.89 (6.3)	7.39 (8.16)	Signed Rank	0.0010
	Median (min;max)	80 (60;102)	71 (58;94)	9 (-12;35)	0.5 (-8;18)	6.5 (-15;21)		
	Q1, Q3 (IQR)	72 85 (13)	65 85 (20)	5 13 (8)	-1 5 (6)	5 12 (7)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0605
	Mean (Std)	77.72 (10.99)	74.56 (11.03)	8.22 (8.67)	3.5 (7.1)	4.72 (9.96)	Signed Rank	0.0079
	Median (min;max)	75.5 (62;102)	70 (62;98)	6.5 (-17;21)	3 (-9;17)	3.5 (-24;23)		
	Q1, Q3 (IQR)	70 85 (15)	66 84 (18)	5 14 (9)	-1 7 (8)	1 10 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1728
	Mean (Std)	77.94 (8.82)	75.06 (13.25)	8.44 (11.02)	4 (7.05)	4.44 (13.25)	Signed Rank	0.0403
	Median (min;max)	75.5 (66;95)	72.5 (59;107)	8.5 (-19;30)	5 (-10;16)	2.5 (-35;26)		
	Q1, Q3 (IQR)	72 84 (12)	64 84 (20)	3 16 (13)	-2 9 (11)	0 12 (12)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5814
	Mean (Std)	77.33 (8.69)	76.94 (13.69)	7.83 (11.19)	5.89 (12.98)	1.94 (14.68)	Signed Rank	0.6013
	Median (min;max)	76 (65;94)	75.5 (59;117)	7 (-22;27)	6 (-29;29)	4.5 (-20;32)		
	Q1, Q3 (IQR)	71 83 (12)	68 80 (12)	3 18 (15)	0 14 (14)	-14 11 (25)		

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Table 14.3-34 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Peppermint 3 mg - 60 min

Time point (min)	Statistics	PSWL60	ZP360	Change in PSWL60	Change in ZP360	Change in PSWL60 - Change in ZP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	71.5 (11.23)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	75 (53;89)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	62 79 (17)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0867
	Mean (Std)	73.72 (7.65)	70.72 (8.91)	4.22 (9.32)	-0.78 (5.98)	5 (11.67)	Signed Rank	0.1110
	Median (min;max)	74 (55;88)	70.5 (58;86)	5 (-13;30)	0 (-12;8)	4 (-15;33)		
	Q1, Q3 (IQR)	70 80 (10)	63 80 (17)	0 8 (8)	-4 4 (8)	-4 11 (15)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0044
	Mean (Std)	79.78 (10.06)	72.78 (9.61)	10.28 (9.6)	1.28 (5.76)	9 (11.64)	Signed Rank	0.0049
	Median (min;max)	80 (60;102)	71.5 (57;91)	9 (-12;35)	2 (-11;9)	10 (-14;36)		
	Q1, Q3 (IQR)	72 85 (13)	66 81 (15)	5 13 (8)	-3 5 (8)	0 16 (16)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0437
	Mean (Std)	77.72 (10.99)	74.33 (11.33)	8.22 (8.67)	2.83 (5)	5.39 (10.49)	Signed Rank	0.0227
	Median (min;max)	75.5 (62;102)	74.5 (58;94)	6.5 (-17;21)	4 (-9;11)	4.5 (-22;26)		
	Q1, Q3 (IQR)	70 85 (15)	65 82 (17)	5 14 (9)	0 6 (6)	0 10 (10)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0510
	Mean (Std)	77.94 (8.82)	73.94 (11.18)	8.44 (11.02)	2.44 (6.11)	6 (12.12)	Signed Rank	0.0441
	Median (min;max)	75.5 (66;95)	75.5 (59;92)	8.5 (-19;30)	1.5 (-9;14)	5.5 (-19;31)		
	Q1, Q3 (IQR)	72 84 (12)	64 84 (20)	3 16 (13)	-1 7 (8)	-3 11 (14)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1793
	Mean (Std)	77.33 (8.69)	75.06 (10.11)	7.83 (11.19)	3.56 (11.02)	4.28 (12.96)	Signed Rank	0.1262
	Median (min;max)	76 (65;94)	75 (56;91)	7 (-22;27)	3 (-19;29)	2 (-21;33)		
	Q1, Q3 (IQR)	71 83 (12)	69 84 (15)	3 18 (15)	-2 9 (11)	0 11 (11)		

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Table 14.3-35 Change in pulse (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Spearmint 3 mg - 60 min

Time point (min)	Statistics	PSWL60	ZSP360	Change in PSWL60	Change in ZSP360	Change in PSWL60 - Change in ZSP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	69.5 (12.07)	71.06 (12.3)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (44;93)	69.5 (54;90)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	63 77 (14)	61 78 (17)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.6011
	Mean (Std)	73.72 (7.65)	73.89 (14.18)	4.22 (9.32)	2.83 (9.67)	1.39 (11.06)	Signed Rank	0.4230
	Median (min;max)	74 (55;88)	74.5 (52;100)	5 (-13;30)	1 (-9;36)	3 (-26;17)		
	Q1, Q3 (IQR)	70 80 (10)	60 81 (21)	0 8 (8)	-2 4 (6)	-2 9 (11)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0037
	Mean (Std)	79.78 (10.06)	73.83 (10.41)	10.28 (9.6)	2.78 (7.07)	7.5 (9.47)	Signed Rank	0.0037
	Median (min;max)	80 (60;102)	75 (59;98)	9 (-12;35)	1.5 (-11;15)	8 (-20;20)		
	Q1, Q3 (IQR)	72 85 (13)	64 80 (16)	5 13 (8)	-1 8 (9)	4 15 (11)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0854
	Mean (Std)	77.72 (10.99)	74.39 (10.91)	8.22 (8.67)	3.33 (8.07)	4.89 (11.35)	Signed Rank	0.0072
	Median (min;max)	75.5 (62;102)	73.5 (60;100)	6.5 (-17;21)	4.5 (-13;15)	6 (-32;19)		
	Q1, Q3 (IQR)	70 85 (15)	68 81 (13)	5 14 (9)	-1 10 (11)	2 11 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1710
	Mean (Std)	77.94 (8.82)	75.72 (11.47)	8.44 (11.02)	4.67 (9.53)	3.78 (11.21)	Signed Rank	0.1860
	Median (min;max)	75.5 (66;95)	73 (61;107)	8.5 (-19;30)	5 (-14;20)	3.5 (-19;19)		
	Q1, Q3 (IQR)	72 84 (12)	69 80 (11)	3 16 (13)	0 11 (11)	-7 15 (22)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9328
	Mean (Std)	77.33 (8.69)	78.61 (13.11)	7.83 (11.19)	7.56 (12.22)	0.28 (13.77)	Signed Rank	0.8085
	Median (min;max)	76 (65;94)	73.5 (60;110)	7 (-22;27)	8 (-13;42)	0.5 (-31;19)		
	Q1, Q3 (IQR)	71 83 (12)	72 83 (11)	3 18 (15)	1 12 (11)	-7 12 (19)		

SM17 01 Analysis of secondary endpoint - Pulse, SAS program: sec endpoint pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:15:52

Table 14.3-36 Change in pulse (beats/min) (pairwise): ZYN[®] Smooth 3 mg - 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	ZS315	ZS3A15	Change in ZS315	Change in ZS3A15	Change in ZS315 - Change in ZS3A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	71.61 (8.25)	70.83 (11.65)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	72.5 (57;89)	70.5 (54;98)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	67 77 (10)	62 76 (14)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1113
	Mean (Std)	74.17 (9.18)	68.83 (12.33)	2.56 (6.26)	-2 (9.23)	4.56 (11.51)	Signed Rank	0.1997
	Median (min;max)	74.5 (56;89)	68 (44;90)	3 (-8;16)	1 (-22;12)	2 (-15;29)		
	Q1, Q3 (IQR)	67 81 (14)	62 78 (16)	-1 7 (8)	-8 4 (12)	-3 12 (15)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1111
	Mean (Std)	76.94 (9.64)	72.83 (10.38)	5.33 (6.32)	2 (7)	3.33 (8.42)	Signed Rank	0.1055
	Median (min;max)	75 (58;96)	72 (59;94)	6 (-7;19)	2 (-12;16)	4.5 (-12;22)		
	Q1, Q3 (IQR)	71 83 (12)	66 79 (13)	0 10 (10)	-4 5 (9)	-3 7 (10)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.6098
	Mean (Std)	78.72 (9.58)	76.67 (9.94)	7.11 (7.05)	5.83 (9.7)	1.28 (10.43)	Signed Rank	0.8446
	Median (min;max)	80 (59;102)	78.5 (60;99)	7 (-9;22)	5 (-16;25)	-1.5 (-16;30)		
	Q1, Q3 (IQR)	74 81 (7)	68 81 (13)	4 14 (10)	1 13 (12)	-4 8 (12)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2353
	Mean (Std)	71.67 (8.37)	67.44 (7.94)	0.06 (6.33)	-3.39 (7.24)	3.44 (11.88)	Signed Rank	0.1175
	Median (min;max)	70.5 (55;92)	65 (50;82)	1 (-18;10)	-3.5 (-20;10)	3.5 (-28;27)		
	Q1, Q3 (IQR)	67 76 (9)	64 72 (8)	-2 4 (6)	-5 1 (6)	-1 7 (8)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8241
	Mean (Std)	68.78 (12.51)	67.28 (10.53)	-2.83 (9.74)	-3.56 (8.69)	0.72 (13.58)	Signed Rank	0.9539
	Median (min;max)	65.5 (52;100)	64.5 (53;93)	-3.5 (-28;18)	-3 (-25;8)	-1.5 (-32;26)		
	Q1, Q3 (IQR)	63 71 (8)	61 69 (8)	-7 0 (7)	-8 4 (12)	-6 6 (12)		

SM17_01 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse_pairwise_extra.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-25T09:03:48

Table 14.3-37 Change in pulse (beats/min) (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	ZS360	ZS3A60	Change in ZS360	Change in ZS3A60	Change in ZS360 - Change in ZS3A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	68.94 (10.04)	70.11 (11.1)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (56;90)	69.5 (46;87)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	62 74 (12)	64 80 (16)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7246
	Mean (Std)	68.89 (11.79)	69.39 (13.27)	-0.06 (6.41)	-0.72 (5.24)	0.67 (7.9)	Signed Rank	0.5431
	Median (min;max)	66 (50;88)	68.5 (48;94)	0 (-12;16)	-1 (-9;10)	2 (-15;14)		
	Q1, Q3 (IQR)	59 80 (21)	60 76 (16)	-3 2 (5)	-5 2 (7)	-3 5 (8)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9014
	Mean (Std)	72.44 (9.9)	73.89 (12.47)	3.5 (7.55)	3.78 (7.3)	-0.28 (9.37)	Signed Rank	0.8084
	Median (min;max)	72 (60;94)	71.5 (60;101)	2.5 (-10;21)	1.5 (-6;18)	1 (-21;13)		
	Q1, Q3 (IQR)	63 79 (16)	64 81 (17)	1 6 (5)	-2 8 (10)	-4 5 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3778
	Mean (Std)	74.94 (12.33)	74.33 (10.1)	6 (8.74)	4.22 (8.54)	1.78 (8.33)	Signed Rank	0.2167
	Median (min;max)	70 (62;98)	72.5 (60;99)	3.5 (-7;29)	3 (-9;27)	2 (-19;15)		
	Q1, Q3 (IQR)	64 87 (23)	70 77 (7)	1 9 (8)	1 7 (6)	-1 7 (8)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2397
	Mean (Std)	76.28 (10.24)	74.94 (11.3)	7.33 (8.46)	4.83 (10.87)	2.5 (8.71)	Signed Rank	0.2582
	Median (min;max)	73.5 (63;97)	74 (57;102)	5.5 (-4;28)	2.5 (-5;40)	1.5 (-12;17)		
	Q1, Q3 (IQR)	69 83 (14)	67 83 (16)	3 8 (5)	-2 8 (10)	-3 9 (12)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.6411
	Mean (Std)	75.72 (13.11)	75.72 (9.41)	6.78 (9.69)	5.61 (8.95)	1.17 (10.43)	Signed Rank	0.8898
	Median (min;max)	73 (58;115)	77 (58;94)	5 (-5;25)	2.5 (-6;22)	-0.5 (-19;21)		
	Q1, Q3 (IQR)	68 82 (14)	70 84 (14)	-3 16 (19)	-1 12 (13)	-6 8 (14)		

SM17_01 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse_pairwise_extra.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-25T09:03:48

Table 14.3-38 Change in pulse (beats/min) (pairwise): ZYN[®] Smooth 6 mg - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	Change in ZS615	ZS6A15	Change in ZS615	ZS6A15	Change in ZS615 - ZS6A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	70.44 (8.97)	70.22 (13.81)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	69.5 (55;86)	67.5 (50;110)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	64 77 (13)	62 77 (15)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9704
	Mean (Std)	71.78 (13.09)	71.67 (11.46)	1.33 (6.82)	1.44 (8.19)	-0.11 (12.53)	Signed Rank	0.8496
	Median (min;max)	70.5 (57;102)	71 (59;95)	0 (-8;16)	0.5 (-15;24)	0 (-32;31)		
	Q1, Q3 (IQR)	60 75 (15)	61 75 (14)	-4 6 (10)	-2 5 (7)	-6 5 (11)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9062
	Mean (Std)	76.5 (12.42)	76.61 (13.45)	6.06 (7.06)	6.39 (9.84)	-0.33 (11.82)	Signed Rank	0.5019
	Median (min;max)	75 (60;111)	75 (54;102)	5.5 (-5;25)	5 (-11;28)	-2 (-18;33)		
	Q1, Q3 (IQR)	68 80 (12)	66 85 (19)	2 10 (8)	1 11 (10)	-6 3 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3097
	Mean (Std)	81.83 (14.34)	78.17 (12.38)	11.39 (9.46)	7.94 (10.37)	3.44 (13.95)	Signed Rank	0.7575
	Median (min;max)	79 (63;125)	78.5 (62;113)	10 (-1;39)	9.5 (-19;24)	-1.5 (-15;36)		
	Q1, Q3 (IQR)	72 91 (19)	66 84 (18)	6 13 (7)	2 13 (11)	-4 10 (14)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.6132
	Mean (Std)	73.17 (9.72)	71.78 (11.62)	2.72 (5.74)	1.56 (6.28)	1.17 (9.61)	Signed Rank	0.6665
	Median (min;max)	70.5 (58;95)	73.5 (55;105)	1.5 (-7;17)	1.5 (-8;14)	0 (-17;25)		
	Q1, Q3 (IQR)	68 82 (14)	64 78 (14)	-1 6 (7)	-3 6 (9)	-3 5 (8)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2755
	Mean (Std)	69.67 (10.21)	66.78 (9.96)	-0.78 (7.34)	-3.44 (7.78)	2.67 (10.04)	Signed Rank	0.4636
	Median (min;max)	66.5 (56;97)	66.5 (53;96)	-1.5 (-18;11)	-2.5 (-17;14)	1 (-14;25)		
	Q1, Q3 (IQR)	65 74 (9)	60 71 (11)	-4 4 (8)	-9 0 (9)	-2 6 (8)		

SM17_01 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse_pairwise_extra.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-25T09:03:48

Table 14.3-39 Change in pulse (beats/min) (pairwise): ZYN[®] Smooth 6 mg - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	ZS660	ZS6A60	Change in ZS660	Change in ZS6A60	Change in ZS660 - Change in ZS6A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	67.61 (9.43)	68.22 (8.88)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	68 (47;91)	66.5 (58;84)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	64 72 (8)	60 76 (16)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1436
	Mean (Std)	68.72 (9.23)	72.67 (9.18)	1.11 (6.79)	4.44 (6.61)	-3.33 (9.22)	Signed Rank	0.2327
	Median (min;max)	68 (49;86)	71.5 (61;87)	0 (-12;13)	4 (-10;17)	-3 (-22;9)		
	Q1, Q3 (IQR)	63 74 (11)	65 81 (16)	-3 6 (9)	2 7 (5)	-9 4 (13)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2260
	Mean (Std)	76.33 (10.12)	79.33 (11.63)	8.72 (7.45)	11.11 (9.55)	-2.39 (8.07)	Signed Rank	0.4252
	Median (min;max)	77 (57;98)	77.5 (62;98)	9 (-6;23)	11 (-6;34)	-1 (-18;10)		
	Q1, Q3 (IQR)	68 84 (16)	71 91 (20)	6 14 (8)	3 16 (13)	-5 4 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5521
	Mean (Std)	74.89 (9.6)	76.83 (11.37)	7.28 (6.33)	8.61 (8.91)	-1.33 (9.32)	Signed Rank	0.5105
	Median (min;max)	75 (56;96)	74 (56;99)	6.5 (-3;19)	8 (-6;23)	0 (-20;21)		
	Q1, Q3 (IQR)	68 81 (13)	70 86 (16)	3 11 (8)	3 16 (13)	-8 3 (11)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3669
	Mean (Std)	75.67 (9.68)	79.22 (13.61)	8.06 (7.33)	11 (13.73)	-2.94 (13.48)	Signed Rank	0.5714
	Median (min;max)	75 (58;94)	76 (61;113)	6.5 (-5;21)	10 (-12;40)	1.5 (-29;14)		
	Q1, Q3 (IQR)	69 84 (15)	69 85 (16)	3 14 (11)	2 20 (18)	-11 7 (18)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8443
	Mean (Std)	76.22 (11.31)	77.22 (11.77)	8.61 (7.59)	9 (11.64)	-0.39 (8.28)	Signed Rank	0.9749
	Median (min;max)	75 (59;110)	76.5 (59;106)	6 (-1;22)	7 (-8;37)	1 (-20;14)		
	Q1, Q3 (IQR)	71 78 (7)	69 83 (14)	3 15 (12)	1 14 (13)	-6 4 (10)		

SM17_01 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse_pairwise_extra.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-25T09:03:48

Table 14.3-40 Change in pulse (beats/min) (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Wintergreen 3 mg - 60 min

Time point (min)	Statistics	ZS360	SW360	Change in ZS360	Change in SW360	Change in ZS360 - Change in SW360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	68.94 (10.04)	68.61 (9.2)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (56;90)	67 (55;87)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	62 74 (12)	60 75 (15)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4866
	Mean (Std)	68.89 (11.79)	70 (11.6)	-0.06 (6.41)	1.39 (4.46)	-1.44 (8.62)	Signed Rank	0.2692
	Median (min;max)	66 (50;88)	71 (53;91)	0 (-12;16)	1 (-6;11)	-1 (-15;21)		
	Q1, Q3 (IQR)	59 80 (21)	61 78 (17)	-3 2 (5)	-2 3 (5)	-6 1 (7)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4085
	Mean (Std)	72.44 (9.9)	74.28 (12.19)	3.5 (7.55)	5.67 (5.55)	-2.17 (10.85)	Signed Rank	0.3690
	Median (min;max)	72 (60;94)	73 (56;105)	2.5 (-10;21)	5 (-4;18)	-1 (-17;16)		
	Q1, Q3 (IQR)	63 79 (16)	67 80 (13)	1 6 (5)	1 8 (7)	-13 5 (18)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9382
	Mean (Std)	74.94 (12.33)	74.39 (11.35)	6 (8.74)	5.78 (6)	0.22 (11.97)	Signed Rank	0.7906
	Median (min;max)	70 (62;98)	71 (62;108)	3.5 (-7;29)	6 (-6;21)	-0.5 (-13;35)		
	Q1, Q3 (IQR)	64 87 (23)	66 81 (15)	1 9 (8)	2 8 (6)	-9 4 (13)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2875
	Mean (Std)	76.28 (10.24)	73.33 (9.31)	7.33 (8.46)	4.72 (4.75)	2.61 (10.09)	Signed Rank	0.3709
	Median (min;max)	73.5 (63;97)	73 (61;97)	5.5 (-4;28)	3 (-1;13)	2 (-16;26)		
	Q1, Q3 (IQR)	69 83 (14)	66 77 (11)	3 8 (5)	1 10 (9)	-4 9 (13)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7486
	Mean (Std)	75.72 (13.11)	74.72 (13.05)	6.78 (9.69)	6.11 (9.15)	0.67 (8.68)	Signed Rank	0.9962
	Median (min;max)	73 (58;115)	75 (55;116)	5 (-5;25)	3.5 (-2;30)	0 (-13;21)		
	Q1, Q3 (IQR)	68 82 (14)	66 79 (13)	-3 16 (19)	1 6 (5)	-5 7 (12)		

SM17_01 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse_pairwise_extra.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-25T09:03:48

Table 14.3-41 Change in pulse (beats/min) (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Peppermint 3 mg - 60 min

Time point (min)	Statistics	ZS360	ZP360	Change in ZS360	Change in ZP360	Change in ZS360 - Change in ZP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	68.94 (10.04)	71.5 (11.23)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (56;90)	75 (53;89)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	62 74 (12)	62 79 (17)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7313
	Mean (Std)	68.89 (11.79)	70.72 (8.91)	-0.06 (6.41)	-0.78 (5.98)	0.72 (8.78)	Signed Rank	0.9450
	Median (min;max)	66 (50;88)	70.5 (58;86)	0 (-12;16)	0 (-12;8)	0 (-10;19)		
	Q1, Q3 (IQR)	59 80 (21)	63 80 (17)	-3 2 (5)	-4 4 (8)	-6 4 (10)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2714
	Mean (Std)	72.44 (9.9)	72.78 (9.61)	3.5 (7.55)	1.28 (5.76)	2.22 (8.29)	Signed Rank	0.3462
	Median (min;max)	72 (60;94)	71.5 (57;91)	2.5 (-10;21)	2 (-11;9)	2 (-12;19)		
	Q1, Q3 (IQR)	63 79 (16)	66 81 (15)	1 6 (5)	-3 5 (8)	-3 6 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2516
	Mean (Std)	74.94 (12.33)	74.33 (11.33)	6 (8.74)	2.83 (5)	3.17 (11.32)	Signed Rank	0.4656
	Median (min;max)	70 (62;98)	74.5 (58;94)	3.5 (-7;29)	4 (-9;11)	-0.5 (-10;34)		
	Q1, Q3 (IQR)	64 87 (23)	65 82 (17)	1 9 (8)	0 6 (6)	-5 10 (15)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0698
	Mean (Std)	76.28 (10.24)	73.94 (11.18)	7.33 (8.46)	2.44 (6.11)	4.89 (10.72)	Signed Rank	0.1572
	Median (min;max)	73.5 (63;97)	75.5 (59;92)	5.5 (-4;28)	1.5 (-9;14)	0.5 (-7;29)		
	Q1, Q3 (IQR)	69 83 (14)	64 84 (20)	3 8 (5)	-1 7 (8)	-4 12 (16)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2744
	Mean (Std)	75.72 (13.11)	75.06 (10.11)	6.78 (9.69)	3.56 (11.02)	3.22 (12.11)	Signed Rank	0.3981
	Median (min;max)	73 (58;115)	75 (56;91)	5 (-5;25)	3 (-19;29)	-3.5 (-11;24)		
	Q1, Q3 (IQR)	68 82 (14)	69 84 (15)	-3 16 (19)	-2 9 (11)	-7 15 (22)		

SM17_01 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse_pairwise_extra.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-25T09:03:48

Table 14.3-42 Change in pulse (beats/min) (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Spearmint 3 mg - 60 min

Time point (min)	Statistics	ZS360	ZSP360	Change in ZS360	Change in ZSP360	Change in ZS360 - Change in ZSP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	68.94 (10.04)	71.06 (12.3)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	66.5 (56;90)	69.5 (54;90)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	62 74 (12)	61 78 (17)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3389
	Mean (Std)	68.89 (11.79)	73.89 (14.18)	-0.06 (6.41)	2.83 (9.67)	-2.89 (12.46)	Signed Rank	0.5519
	Median (min;max)	66 (50;88)	74.5 (52;100)	0 (-12;16)	1 (-9;36)	-1 (-48;10)		
	Q1, Q3 (IQR)	59 80 (21)	60 81 (21)	-3 2 (5)	-2 4 (6)	-5 4 (9)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7348
	Mean (Std)	72.44 (9.9)	73.83 (10.41)	3.5 (7.55)	2.78 (7.07)	0.72 (8.9)	Signed Rank	0.8399
	Median (min;max)	72 (60;94)	75 (59;98)	2.5 (-10;21)	1.5 (-11;15)	-2 (-10;16)		
	Q1, Q3 (IQR)	63 79 (16)	64 80 (16)	1 6 (5)	-1 8 (9)	-7 12 (19)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1901
	Mean (Std)	74.94 (12.33)	74.39 (10.91)	6 (8.74)	3.33 (8.07)	2.67 (8.29)	Signed Rank	0.3339
	Median (min;max)	70 (62;98)	73.5 (60;100)	3.5 (-7;29)	4.5 (-13;15)	1.5 (-8;22)		
	Q1, Q3 (IQR)	64 87 (23)	68 81 (13)	1 9 (8)	-1 10 (11)	-2 7 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3492
	Mean (Std)	76.28 (10.24)	75.72 (11.47)	7.33 (8.46)	4.67 (9.53)	2.67 (11.75)	Signed Rank	0.5710
	Median (min;max)	73.5 (63;97)	73 (61;107)	5.5 (-4;28)	5 (-14;20)	-0.5 (-17;29)		
	Q1, Q3 (IQR)	69 83 (14)	69 80 (11)	3 8 (5)	0 11 (11)	-6 12 (18)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7646
	Mean (Std)	75.72 (13.11)	78.61 (13.11)	6.78 (9.69)	7.56 (12.22)	-0.78 (10.84)	Signed Rank	0.9909
	Median (min;max)	73 (58;115)	73.5 (60;110)	5 (-5;25)	8 (-13;42)	1.5 (-23;15)		
	Q1, Q3 (IQR)	68 82 (14)	72 83 (11)	-3 16 (19)	1 12 (11)	-7 8 (15)		

SM17_01 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse_pairwise_extra.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-25T09:03:48

Table 14.3-43 Summary statistics of relative nicotine effect (VAS rating) by treatment

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
Subjective nicotine effect (VAS rating)	Measured value	Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	42	7.61	4	11.9
			Timepoint 0:10	18	0	44	10.7	6.5	12.1
			Timepoint 0:15	18	0	40	10.6	6.5	11.7
			Timepoint 0:30	18	0	24	2.44	0	5.87
			Timepoint 1:00	18	0	10	0.667	0	2.38
		Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	56	6.89	3.5	13.4
			Timepoint 0:10	18	0	45	12.7	9.5	13.3
			Timepoint 0:15	18	0	44	13.1	10.5	11.6
			Timepoint 0:30	18	0	34	10.4	7	10.6
			Timepoint 1:00	18	0	24	6.17	1.5	8.04
		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	28	5.06	3	7.56
			Timepoint 0:10	18	0	23	8.72	5	8.29
			Timepoint 0:15	18	0	26	9	5.5	8.4
			Timepoint 0:30	18	0	38	8.78	5	10.6
			Timepoint 1:00	18	0	15	1.72	0	4.04
		ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	43	5.28	1	10.2
			Timepoint 0:10	18	0	57	11.2	3	17.1
			Timepoint 0:15	18	0	45	11.9	5	14.7
			Timepoint 0:30	18	0	26	1.83	0	6.14
			Timepoint 1:00	18	0	0	0	0	0
ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	0	0	0	0	0		
	Timepoint 0:05	18	0	37	5.56	0	10.1		

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
			Timepoint 0:10	18	0	39	9.61	2	13.5
			Timepoint 0:15	18	0	42	9.5	3	14.3
			Timepoint 0:30	18	0	34	8.17	4.5	9.87
			Timepoint 1:00	18	0	23	2.67	0	6.77
		ZYN® Smooth 3 mg - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	14	4.89	4.5	4.66
			Timepoint 0:10	18	0	39	11.1	5.5	12.5
			Timepoint 0:15	18	0	40	12.6	5.5	14.6
			Timepoint 0:30	18	0	17	2.33	0	4.67
			Timepoint 1:00	18	0	0	0	0	0
		ZYN® Smooth 3 mg - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	25	5.06	0	8.39
			Timepoint 0:10	18	0	36	8.67	0.5	12.1
			Timepoint 0:15	18	0	37	11.1	7.5	12.3
			Timepoint 0:30	18	0	32	7.5	4	9.53
			Timepoint 1:00	18	0	17	2.39	0	4.29
		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	27	5.44	2	8.41
			Timepoint 0:10	18	0	76	15.3	5	22.2
			Timepoint 0:15	18	0	81	12.4	4	20.1
			Timepoint 0:30	18	0	24	2.83	0	7.39
			Timepoint 1:00	18	0	67	4.33	0	15.7
		ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	42	7	2.5	10.8
			Timepoint 0:10	18	0	64	13.3	9	16.4
			Timepoint 0:15	18	0	58	12.6	6.5	16.9
			Timepoint 0:30	18	0	49	11.9	6.5	14.6

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Smooth 6 mg - 15 min	Timepoint 1:00	18	0	24	4.44	0.5	6.71
			Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	45	9.5	4	14.1
			Timepoint 0:10	18	0	56	13.4	5.5	19
			Timepoint 0:15	18	0	55	14.3	7	16.8
			Timepoint 0:30	18	0	27	4.39	0	8.54
		ZYN® Smooth 6 mg - 60 min	Timepoint 1:00	18	0	0	0	0	0
			Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	18	6.22	7.5	6.01
			Timepoint 0:10	18	0	49	13.3	9	14.3
			Timepoint 0:15	18	0	42	14.3	10.5	12.6
			Timepoint 0:30	18	0	49	12.6	9.5	12.5
			Timepoint 1:00	18	0	24	7	4	8.41
		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	24	3.11	0	6.43
			Timepoint 0:10	18	0	23	5.33	2.5	6.95
			Timepoint 0:15	18	0	21	5.67	4	6.62
			Timepoint 0:30	18	0	21	6.17	5.5	6.69
			Timepoint 1:00	18	0	15	1.17	0	3.59
		ZYN® Wintergreen 3 mg (Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	30	5	2	8.25
			Timepoint 0:10	18	0	35	7.17	4.5	9.4
			Timepoint 0:15	18	0	29	7.11	4.5	9.03
			Timepoint 0:30	18	0	30	6.94	4.5	9.42
			Timepoint 1:00	18	0	29	4.06	0	8.64
		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	33	4.17	0	9.43

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
			Timepoint 0:10	18	0	52	10.1	4	14.2
			Timepoint 0:15	18	0	51	10.4	5.5	13.3
			Timepoint 0:30	18	0	47	10.4	4.5	15.5
			Timepoint 1:00	18	0	20	1.5	0	4.83
	Absolute change from pre-dose baseline	Swedish portion snus PSWL 1.0 g (8 mg) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	42	7.61	4	11.9
			Timepoint 0:10	18	0	44	10.7	6.5	12.1
			Timepoint 0:15	18	0	40	10.6	6.5	11.7
			Timepoint 0:30	18	0	24	2.44	0	5.87
			Timepoint 1:00	18	0	10	0.667	0	2.38
		Swedish portion snus PSWL 1.0 g (8 mg) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	56	6.89	3.5	13.4
			Timepoint 0:10	18	0	45	12.7	9.5	13.3
			Timepoint 0:15	18	0	44	13.1	10.5	11.6
			Timepoint 0:30	18	0	34	10.4	7	10.6
			Timepoint 1:00	18	0	24	6.17	1.5	8.04
		ZYN® Peppermint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	28	5.06	3	7.56
			Timepoint 0:10	18	0	23	8.72	5	8.29
			Timepoint 0:15	18	0	26	9	5.5	8.4
			Timepoint 0:30	18	0	38	8.78	5	10.6
			Timepoint 1:00	18	0	15	1.72	0	4.04
		ZYN® Smooth 3 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	43	5.28	1	10.2
			Timepoint 0:10	18	0	57	11.2	3	17.1
			Timepoint 0:15	18	0	45	11.9	5	14.7
			Timepoint 0:30	18	0	26	1.83	0	6.14

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Smooth 3 mg (alt. manu. proc.) - 60 min	Timepoint 1:00	18	0	0	0	0	0
			Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	37	5.56	0	10.1
			Timepoint 0:10	18	0	39	9.61	2	13.5
			Timepoint 0:15	18	0	42	9.5	3	14.3
			Timepoint 0:30	18	0	34	8.17	4.5	9.87
		ZYN® Smooth 3 mg - 15 min	Timepoint 1:00	18	0	23	2.67	0	6.77
			Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	14	4.89	4.5	4.66
			Timepoint 0:10	18	0	39	11.1	5.5	12.5
			Timepoint 0:15	18	0	40	12.6	5.5	14.6
			Timepoint 0:30	18	0	17	2.33	0	4.67
		ZYN® Smooth 3 mg - 60 min	Timepoint 1:00	18	0	0	0	0	0
			Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	25	5.06	0	8.39
			Timepoint 0:10	18	0	36	8.67	0.5	12.1
			Timepoint 0:15	18	0	37	11.1	7.5	12.3
			Timepoint 0:30	18	0	32	7.5	4	9.53
			Timepoint 1:00	18	0	17	2.39	0	4.29
		ZYN® Smooth 6 mg (alt. manu. proc.) - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	27	5.44	2	8.41
			Timepoint 0:10	18	0	76	15.3	5	22.2
			Timepoint 0:15	18	0	81	12.4	4	20.1
			Timepoint 0:30	18	0	24	2.83	0	7.39
			Timepoint 1:00	18	0	67	4.33	0	15.7
		ZYN® Smooth 6 mg (alt. manu. proc.) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	42	7	2.5	10.8

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
			Timepoint 0:10	18	0	64	13.3	9	16.4
			Timepoint 0:15	18	0	58	12.6	6.5	16.9
			Timepoint 0:30	18	0	49	11.9	6.5	14.6
			Timepoint 1:00	18	0	24	4.44	0.5	6.71
		ZYN® Smooth 6 mg - 15 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	45	9.5	4	14.1
			Timepoint 0:10	18	0	56	13.4	5.5	19
			Timepoint 0:15	18	0	55	14.3	7	16.8
			Timepoint 0:30	18	0	27	4.39	0	8.54
			Timepoint 1:00	18	0	0	0	0	0
		ZYN® Smooth 6 mg - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	18	6.22	7.5	6.01
			Timepoint 0:10	18	0	49	13.3	9	14.3
			Timepoint 0:15	18	0	42	14.3	10.5	12.6
			Timepoint 0:30	18	0	49	12.6	9.5	12.5
			Timepoint 1:00	18	0	24	7	4	8.41
		ZYN® Spearmint 3 mg (Nicotine and Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	24	3.11	0	6.43
			Timepoint 0:10	18	0	23	5.33	2.5	6.95
			Timepoint 0:15	18	0	21	5.67	4	6.62
			Timepoint 0:30	18	0	21	6.17	5.5	6.69
			Timepoint 1:00	18	0	15	1.17	0	3.59
		ZYN® Wintergreen 3 mg (Flavor) - 60 min	Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	30	5	2	8.25
			Timepoint 0:10	18	0	35	7.17	4.5	9.4
			Timepoint 0:15	18	0	29	7.11	4.5	9.03
			Timepoint 0:30	18	0	30	6.94	4.5	9.42

Laboratory test name	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		ZYN® Wintergreen 3 mg (Nicotine) - 60 min	Timepoint 1:00	18	0	29	4.06	0	8.64
			Timepoint 0:00	18	0	0	0	0	0
			Timepoint 0:05	18	0	33	4.17	0	9.43
			Timepoint 0:10	18	0	52	10.1	4	14.2
			Timepoint 0:15	18	0	51	10.4	5.5	13.3
			Timepoint 0:30	18	0	47	10.4	4.5	15.5
			Timepoint 1:00	18	0	20	1.5	0	4.83

SM17_01 QS tabulations, SAS program: safety_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:36:14

Table 14.3-44 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 3 mg - 15 min

Time point (min)	Statistics	PSWL15	ZS315	Change in PSWL15	Change in ZS315	Change in PSWL15 - Change in ZS315	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3559
	Mean (Std)	7.61 (11.94)	4.89 (4.66)	7.61 (11.94)	4.89 (4.66)	2.72 (12.17)	Signed Rank	0.5883
	Median (min;max)	4 (0;42)	4.5 (0;14)	4 (0;42)	4.5 (0;14)	0.5 (-14;35)		
	Q1, Q3 (IQR)	0 9 (9)	0 8 (8)	0 9 (9)	0 8 (8)	-2 5 (7)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9067
	Mean (Std)	10.67 (12.14)	11.06 (12.46)	10.67 (12.14)	11.06 (12.46)	-0.39 (13.87)	Signed Rank	0.8701
	Median (min;max)	6.5 (0;44)	5.5 (0;39)	6.5 (0;44)	5.5 (0;39)	1 (-23;34)		
	Q1, Q3 (IQR)	5 10 (5)	2 23 (21)	5 10 (5)	2 23 (21)	-8 4 (12)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5850
	Mean (Std)	10.61 (11.72)	12.56 (14.6)	10.61 (11.72)	12.56 (14.6)	-1.94 (14.82)	Signed Rank	0.5704
	Median (min;max)	6.5 (0;40)	5.5 (0;40)	6.5 (0;40)	5.5 (0;40)	0.5 (-31;40)		
	Q1, Q3 (IQR)	4 15 (11)	1 30 (29)	4 15 (11)	1 30 (29)	-10 4 (14)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9529
	Mean (Std)	2.44 (5.87)	2.33 (4.67)	2.44 (5.87)	2.33 (4.67)	0.11 (7.87)	Signed Rank	0.9844
	Median (min;max)	0 (0;24)	0 (0;17)	0 (0;24)	0 (0;17)	0 (-17;24)		
	Q1, Q3 (IQR)	0 2 (2)	0 2 (2)	0 2 (2)	0 2 (2)	-2 2 (4)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2503
	Mean (Std)	0.67 (2.38)	0 (0)	0.67 (2.38)	0 (0)	0.67 (2.38)	Signed Rank	0.5000
	Median (min;max)	0 (0;10)	0 (0;0)	0 (0;10)	0 (0;0)	0 (0;10)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		

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Table 14.3-45 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 6 mg - 15 min

Time point (min)	Statistics	PSWL15	ZS615	Change in PSWL15	Change in ZS615	Change in PSWL15 - Change in ZS615	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2518
	Mean (Std)	7.61 (11.94)	9.5 (14.13)	7.61 (11.94)	9.5 (14.13)	-1.89 (6.76)	Signed Rank	0.4580
	Median (min;max)	4 (0;42)	4 (0;45)	4 (0;42)	4 (0;45)	0 (-20;8)		
	Q1, Q3 (IQR)	0 9 (9)	1 9 (8)	0 9 (9)	1 9 (8)	-3 1 (4)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3273
	Mean (Std)	10.67 (12.14)	13.44 (18.98)	10.67 (12.14)	13.44 (18.98)	-2.78 (11.68)	Signed Rank	0.9904
	Median (min;max)	6.5 (0;44)	5.5 (0;56)	6.5 (0;44)	5.5 (0;56)	0.5 (-36;9)		
	Q1, Q3 (IQR)	5 10 (5)	1 18 (17)	5 10 (5)	1 18 (17)	-4 4 (8)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0615
	Mean (Std)	10.61 (11.72)	14.28 (16.79)	10.61 (11.72)	14.28 (16.79)	-3.67 (7.77)	Signed Rank	0.1113
	Median (min;max)	6.5 (0;40)	7 (0;55)	6.5 (0;40)	7 (0;55)	-2.5 (-19;8)		
	Q1, Q3 (IQR)	4 15 (11)	4 20 (16)	4 15 (11)	4 20 (16)	-7 2 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2361
	Mean (Std)	2.44 (5.87)	4.39 (8.54)	2.44 (5.87)	4.39 (8.54)	-1.94 (6.72)	Signed Rank	0.2930
	Median (min;max)	0 (0;24)	0 (0;27)	0 (0;24)	0 (0;27)	0 (-27;5)		
	Q1, Q3 (IQR)	0 2 (2)	0 4 (4)	0 2 (2)	0 4 (4)	-2 0 (2)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2503
	Mean (Std)	0.67 (2.38)	0 (0)	0.67 (2.38)	0 (0)	0.67 (2.38)	Signed Rank	0.5000
	Median (min;max)	0 (0;10)	0 (0;0)	0 (0;10)	0 (0;0)	0 (0;10)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		

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Table 14.3-46 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	Change in PSWL15	ZS3A15	Change in PSWL15	ZS3A15	Change in PSWL15 - ZS3A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1413
	Mean (Std)	7.61 (11.94)	5.28 (10.22)	7.61 (11.94)	5.28 (10.22)	2.33 (6.42)	Signed Rank	0.2095
	Median (min;max)	4 (0;42)	1 (0;43)	4 (0;42)	1 (0;43)	0 (-7;21)		
	Q1, Q3 (IQR)	0 9 (9)	0 7 (7)	0 9 (9)	0 7 (7)	-1 4 (5)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7999
	Mean (Std)	10.67 (12.14)	11.22 (17.09)	10.67 (12.14)	11.22 (17.09)	-0.56 (9.15)	Signed Rank	0.2794
	Median (min;max)	6.5 (0;44)	3 (0;57)	6.5 (0;44)	3 (0;57)	2 (-30;9)		
	Q1, Q3 (IQR)	5 10 (5)	0 21 (21)	5 10 (5)	0 21 (21)	0 3 (3)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5611
	Mean (Std)	10.61 (11.72)	11.94 (14.65)	10.61 (11.72)	11.94 (14.65)	-1.33 (9.54)	Signed Rank	0.8674
	Median (min;max)	6.5 (0;40)	5 (0;45)	6.5 (0;40)	5 (0;45)	0 (-29;16)		
	Q1, Q3 (IQR)	4 15 (11)	1 21 (20)	4 15 (11)	1 21 (20)	-5 4 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7764
	Mean (Std)	2.44 (5.87)	1.83 (6.14)	2.44 (5.87)	1.83 (6.14)	0.61 (8.98)	Signed Rank	0.6328
	Median (min;max)	0 (0;24)	0 (0;26)	0 (0;24)	0 (0;26)	0 (-26;24)		
	Q1, Q3 (IQR)	0 2 (2)	0 0 (0)	0 2 (2)	0 0 (0)	0 2 (2)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2503
	Mean (Std)	0.67 (2.38)	0 (0)	0.67 (2.38)	0 (0)	0.67 (2.38)	Signed Rank	0.5000
	Median (min;max)	0 (0;10)	0 (0;0)	0 (0;10)	0 (0;0)	0 (0;10)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		

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Table 14.3-47 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	PSWL15	ZS6A15	Change in PSWL15	Change in ZS6A15	Change in PSWL15 - Change in ZS6A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2842
	Mean (Std)	7.61 (11.94)	5.44 (8.41)	7.61 (11.94)	5.44 (8.41)	2.17 (8.31)	Signed Rank	0.2463
	Median (min;max)	4 (0;42)	2 (0;27)	4 (0;42)	2 (0;27)	1 (-16;22)		
	Q1, Q3 (IQR)	0 9 (9)	0 8 (8)	0 9 (9)	0 8 (8)	-2 6 (8)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2023
	Mean (Std)	10.67 (12.14)	15.33 (22.2)	10.67 (12.14)	15.33 (22.2)	-4.67 (14.93)	Signed Rank	0.7959
	Median (min;max)	6.5 (0;44)	5 (0;76)	6.5 (0;44)	5 (0;76)	0 (-48;9)		
	Q1, Q3 (IQR)	5 10 (5)	2 25 (23)	5 10 (5)	2 25 (23)	-3 3 (6)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5466
	Mean (Std)	10.61 (11.72)	12.39 (20.1)	10.61 (11.72)	12.39 (20.1)	-1.78 (12.26)	Signed Rank	0.9388
	Median (min;max)	6.5 (0;40)	4 (0;81)	6.5 (0;40)	4 (0;81)	0.5 (-44;13)		
	Q1, Q3 (IQR)	4 15 (11)	0 20 (20)	4 15 (11)	0 20 (20)	-4 4 (8)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8552
	Mean (Std)	2.44 (5.87)	2.83 (7.39)	2.44 (5.87)	2.83 (7.39)	-0.39 (8.91)	Signed Rank	1.0000
	Median (min;max)	0 (0;24)	0 (0;24)	0 (0;24)	0 (0;24)	0 (-24;24)		
	Q1, Q3 (IQR)	0 2 (2)	0 0 (0)	0 2 (2)	0 0 (0)	0 2 (2)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3480
	Mean (Std)	0.67 (2.38)	4.33 (15.75)	0.67 (2.38)	4.33 (15.75)	-3.67 (16.12)	Signed Rank	0.6250
	Median (min;max)	0 (0;10)	0 (0;67)	0 (0;10)	0 (0;67)	0 (-67;10)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		

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Table 14.3-48 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 3 mg - 60 min

Time point (min)	Statistics	PSWL60	ZS360	Change in PSWL60	Change in ZS360	Change in PSWL60 - Change in ZS360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4628
	Mean (Std)	6.89 (13.43)	5.06 (8.39)	6.89 (13.43)	5.06 (8.39)	1.83 (10.35)	Signed Rank	0.3145
	Median (min;max)	3.5 (0;56)	0 (0;25)	3.5 (0;56)	0 (0;25)	0 (-20;36)		
	Q1, Q3 (IQR)	0 7 (7)	0 6 (6)	0 7 (7)	0 6 (6)	0 3 (3)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0650
	Mean (Std)	12.67 (13.27)	8.67 (12.07)	12.67 (13.27)	8.67 (12.07)	4 (8.6)	Signed Rank	0.0428
	Median (min;max)	9.5 (0;45)	0.5 (0;36)	9.5 (0;45)	0.5 (0;36)	3 (-17;23)		
	Q1, Q3 (IQR)	3 16 (13)	0 18 (18)	3 16 (13)	0 18 (18)	0 10 (10)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4696
	Mean (Std)	13.11 (11.63)	11.06 (12.31)	13.11 (11.63)	11.06 (12.31)	2.06 (11.79)	Signed Rank	0.3825
	Median (min;max)	10.5 (0;44)	7.5 (0;37)	10.5 (0;44)	7.5 (0;37)	1 (-20;32)		
	Q1, Q3 (IQR)	4 18 (14)	0 20 (20)	4 18 (14)	0 20 (20)	-2 8 (10)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3465
	Mean (Std)	10.39 (10.6)	7.5 (9.53)	10.39 (10.6)	7.5 (9.53)	2.89 (12.66)	Signed Rank	0.3389
	Median (min;max)	7 (0;34)	4 (0;32)	7 (0;34)	4 (0;32)	2.5 (-20;29)		
	Q1, Q3 (IQR)	3 13 (10)	0 13 (13)	3 13 (10)	0 13 (13)	-2 8 (10)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0317
	Mean (Std)	6.17 (8.04)	2.39 (4.29)	6.17 (8.04)	2.39 (4.29)	3.78 (6.85)	Signed Rank	0.0283
	Median (min;max)	1.5 (0;24)	0 (0;17)	1.5 (0;24)	0 (0;17)	0 (-4;21)		
	Q1, Q3 (IQR)	0 10 (10)	0 4 (4)	0 10 (10)	0 4 (4)	0 7 (7)		

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Table 14.3-49 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 6 mg - 60 min

Time point (min)	Statistics	PSWL60	ZS660	Change in PSWL60	Change in ZS660	Change in PSWL60 - Change in ZS660	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8491
	Mean (Std)	6.89 (13.43)	6.22 (6.01)	6.89 (13.43)	6.22 (6.01)	0.67 (14.64)	Signed Rank	0.2283
	Median (min;max)	3.5 (0;56)	7.5 (0;18)	3.5 (0;56)	7.5 (0;18)	-1 (-12;56)		
	Q1, Q3 (IQR)	0 7 (7)	0 10 (10)	0 7 (7)	0 10 (10)	-6 0 (6)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8430
	Mean (Std)	12.67 (13.27)	13.33 (14.35)	12.67 (13.27)	13.33 (14.35)	-0.67 (14.07)	Signed Rank	0.4099
	Median (min;max)	9.5 (0;45)	9 (0;49)	9.5 (0;45)	9 (0;49)	-2 (-19;45)		
	Q1, Q3 (IQR)	3 16 (13)	3 19 (16)	3 16 (13)	3 19 (16)	-7 4 (11)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5019
	Mean (Std)	13.11 (11.63)	14.33 (12.56)	13.11 (11.63)	14.33 (12.56)	-1.22 (7.56)	Signed Rank	0.5025
	Median (min;max)	10.5 (0;44)	10.5 (0;42)	10.5 (0;44)	10.5 (0;42)	0 (-17;17)		
	Q1, Q3 (IQR)	4 18 (14)	5 24 (19)	4 18 (14)	5 24 (19)	-6 3 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4013
	Mean (Std)	10.39 (10.6)	12.56 (12.51)	10.39 (10.6)	12.56 (12.51)	-2.17 (10.68)	Signed Rank	0.6273
	Median (min;max)	7 (0;34)	9.5 (0;49)	7 (0;34)	9.5 (0;49)	0 (-34;8)		
	Q1, Q3 (IQR)	3 13 (10)	3 20 (17)	3 13 (10)	3 20 (17)	-8 6 (14)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.6906
	Mean (Std)	6.17 (8.04)	7 (8.41)	6.17 (8.04)	7 (8.41)	-0.83 (8.73)	Signed Rank	0.8811
	Median (min;max)	1.5 (0;24)	4 (0;24)	1.5 (0;24)	4 (0;24)	0 (-23;14)		
	Q1, Q3 (IQR)	0 10 (10)	0 12 (12)	0 10 (10)	0 12 (12)	-4 3 (7)		

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Table 14.3-50 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	PSWL60	ZS3A60	Change in PSWL60	Change in ZS3A60	Change in PSWL60 - Change in ZS3A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5307
	Mean (Std)	6.89 (13.43)	5.56 (10.13)	6.89 (13.43)	5.56 (10.13)	1.33 (8.84)	Signed Rank	0.2676
	Median (min;max)	3.5 (0;56)	0 (0;37)	3.5 (0;56)	0 (0;37)	0 (-26;19)		
	Q1, Q3 (IQR)	0 7 (7)	0 7 (7)	0 7 (7)	0 7 (7)	0 5 (5)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0972
	Mean (Std)	12.67 (13.27)	9.61 (13.51)	12.67 (13.27)	9.61 (13.51)	3.06 (7.38)	Signed Rank	0.0751
	Median (min;max)	9.5 (0;45)	2 (0;39)	9.5 (0;45)	2 (0;39)	2.5 (-14;17)		
	Q1, Q3 (IQR)	3 16 (13)	0 19 (19)	3 16 (13)	0 19 (19)	0 9 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0369
	Mean (Std)	13.11 (11.63)	9.5 (14.31)	13.11 (11.63)	9.5 (14.31)	3.61 (6.77)	Signed Rank	0.0558
	Median (min;max)	10.5 (0;44)	3 (0;42)	10.5 (0;44)	3 (0;42)	4.5 (-10;15)		
	Q1, Q3 (IQR)	4 18 (14)	0 10 (10)	4 18 (14)	0 10 (10)	0 8 (8)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1006
	Mean (Std)	10.39 (10.6)	8.17 (9.87)	10.39 (10.6)	8.17 (9.87)	2.22 (5.43)	Signed Rank	0.1155
	Median (min;max)	7 (0;34)	4.5 (0;34)	7 (0;34)	4.5 (0;34)	1 (-6;16)		
	Q1, Q3 (IQR)	3 13 (10)	0 10 (10)	3 13 (10)	0 10 (10)	0 6 (6)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1214
	Mean (Std)	6.17 (8.04)	2.67 (6.77)	6.17 (8.04)	2.67 (6.77)	3.5 (9.11)	Signed Rank	0.1523
	Median (min;max)	1.5 (0;24)	0 (0;23)	1.5 (0;24)	0 (0;23)	0 (-9;24)		
	Q1, Q3 (IQR)	0 10 (10)	0 0 (0)	0 10 (10)	0 0 (0)	0 6 (6)		

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Table 14.3-51 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	PSWL60	ZS6A60	Change in PSWL60	Change in ZS6A60	Change in PSWL60 - Change in ZS6A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9766
	Mean (Std)	6.89 (13.43)	7 (10.78)	6.89 (13.43)	7 (10.78)	-0.11 (15.86)	Signed Rank	0.7813
	Median (min;max)	3.5 (0;56)	2.5 (0;42)	3.5 (0;56)	2.5 (0;42)	0 (-42;42)		
	Q1, Q3 (IQR)	0 7 (7)	0 10 (10)	0 7 (7)	0 10 (10)	-1 2 (3)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8127
	Mean (Std)	12.67 (13.27)	13.28 (16.4)	12.67 (13.27)	13.28 (16.4)	-0.61 (10.77)	Signed Rank	0.7526
	Median (min;max)	9.5 (0;45)	9 (0;64)	9.5 (0;45)	9 (0;64)	1 (-32;14)		
	Q1, Q3 (IQR)	3 16 (13)	3 13 (10)	3 16 (13)	3 13 (10)	-3 6 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7766
	Mean (Std)	13.11 (11.63)	12.56 (16.94)	13.11 (11.63)	12.56 (16.94)	0.56 (8.18)	Signed Rank	0.4910
	Median (min;max)	10.5 (0;44)	6.5 (0;58)	10.5 (0;44)	6.5 (0;58)	2 (-24;12)		
	Q1, Q3 (IQR)	4 18 (14)	2 16 (14)	4 18 (14)	2 16 (14)	-4 4 (8)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5686
	Mean (Std)	10.39 (10.6)	11.89 (14.57)	10.39 (10.6)	11.89 (14.57)	-1.5 (10.95)	Signed Rank	0.6089
	Median (min;max)	7 (0;34)	6.5 (0;49)	7 (0;34)	6.5 (0;49)	0 (-25;26)		
	Q1, Q3 (IQR)	3 13 (10)	2 15 (13)	3 13 (10)	2 15 (13)	-8 4 (12)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0704
	Mean (Std)	6.17 (8.04)	4.44 (6.71)	6.17 (8.04)	4.44 (6.71)	1.72 (3.79)	Signed Rank	0.1055
	Median (min;max)	1.5 (0;24)	0.5 (0;24)	1.5 (0;24)	0.5 (0;24)	0 (-4;10)		
	Q1, Q3 (IQR)	0 10 (10)	0 7 (7)	0 10 (10)	0 7 (7)	0 3 (3)		

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Table 14.3-52 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Wintergreen (nicotine) 3 mg - 60 min

Time point (min)	Statistics	PSWL60	SW360	Change in PSWL60	Change in SW360	Change in PSWL60 - Change in SW360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3502
	Mean (Std)	6.89 (13.43)	4.17 (9.43)	6.89 (13.43)	4.17 (9.43)	2.72 (12.02)	Signed Rank	0.0713
	Median (min;max)	3.5 (0;56)	0 (0;33)	3.5 (0;56)	0 (0;33)	0.5 (-33;30)		
	Q1, Q3 (IQR)	0 7 (7)	0 3 (3)	0 7 (7)	0 3 (3)	0 6 (6)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2333
	Mean (Std)	12.67 (13.27)	10.11 (14.25)	12.67 (13.27)	10.11 (14.25)	2.56 (8.77)	Signed Rank	0.1479
	Median (min;max)	9.5 (0;45)	4 (0;52)	9.5 (0;45)	4 (0;52)	3.5 (-20;16)		
	Q1, Q3 (IQR)	3 16 (13)	0 19 (19)	3 16 (13)	0 19 (19)	-1 9 (10)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1485
	Mean (Std)	13.11 (11.63)	10.44 (13.33)	13.11 (11.63)	10.44 (13.33)	2.67 (7.48)	Signed Rank	0.0654
	Median (min;max)	10.5 (0;44)	5.5 (0;51)	10.5 (0;44)	5.5 (0;51)	3.5 (-17;20)		
	Q1, Q3 (IQR)	4 18 (14)	0 14 (14)	4 18 (14)	0 14 (14)	0 5 (5)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	1.0000
	Mean (Std)	10.39 (10.6)	10.39 (15.49)	10.39 (10.6)	10.39 (15.49)	0 (12.25)	Signed Rank	0.3809
	Median (min;max)	7 (0;34)	4.5 (0;47)	7 (0;34)	4.5 (0;47)	3.5 (-34;21)		
	Q1, Q3 (IQR)	3 13 (10)	0 9 (9)	3 13 (10)	0 9 (9)	0 6 (6)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0344
	Mean (Std)	6.17 (8.04)	1.5 (4.83)	6.17 (8.04)	1.5 (4.83)	4.67 (8.61)	Signed Rank	0.0391
	Median (min;max)	1.5 (0;24)	0 (0;20)	1.5 (0;24)	0 (0;20)	0 (-10;24)		
	Q1, Q3 (IQR)	0 10 (10)	0 0 (0)	0 10 (10)	0 0 (0)	0 8 (8)		

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Table 14.3-53 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Wintergreen (flavor) 3 mg - 60 min

Time point (min)	Statistics	PSWL60	SW360F	Change in PSWL60	Change in SW360F	Change in PSWL60 - Change in SW360F	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4463
	Mean (Std)	6.89 (13.43)	5 (8.25)	6.89 (13.43)	5 (8.25)	1.89 (10.28)	Signed Rank	0.5298
	Median (min;max)	3.5 (0;56)	2 (0;30)	3.5 (0;56)	2 (0;30)	0 (-20;26)		
	Q1, Q3 (IQR)	0 7 (7)	0 5 (5)	0 7 (7)	0 5 (5)	-1 5 (6)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0160
	Mean (Std)	12.67 (13.27)	7.17 (9.4)	12.67 (13.27)	7.17 (9.4)	5.5 (8.73)	Signed Rank	0.0115
	Median (min;max)	9.5 (0;45)	4.5 (0;35)	9.5 (0;45)	4.5 (0;35)	2.5 (-5;26)		
	Q1, Q3 (IQR)	3 16 (13)	0 9 (9)	3 16 (13)	0 9 (9)	0 9 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	<.0001
	Mean (Std)	13.11 (11.63)	7.11 (9.03)	13.11 (11.63)	7.11 (9.03)	6 (4.55)	Signed Rank	<.0001
	Median (min;max)	10.5 (0;44)	4.5 (0;29)	10.5 (0;44)	4.5 (0;29)	6.5 (0;16)		
	Q1, Q3 (IQR)	4 18 (14)	0 10 (10)	4 18 (14)	0 10 (10)	3 8 (5)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1187
	Mean (Std)	10.39 (10.6)	6.94 (9.42)	10.39 (10.6)	6.94 (9.42)	3.44 (8.89)	Signed Rank	0.0309
	Median (min;max)	7 (0;34)	4.5 (0;30)	7 (0;34)	4.5 (0;30)	5 (-20;26)		
	Q1, Q3 (IQR)	3 13 (10)	0 6 (6)	3 13 (10)	0 6 (6)	-1 8 (9)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1297
	Mean (Std)	6.17 (8.04)	4.06 (8.64)	6.17 (8.04)	4.06 (8.64)	2.11 (5.62)	Signed Rank	0.2207
	Median (min;max)	1.5 (0;24)	0 (0;29)	1.5 (0;24)	0 (0;29)	0 (-5;17)		
	Q1, Q3 (IQR)	0 10 (10)	0 4 (4)	0 10 (10)	0 4 (4)	0 3 (3)		

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Table 14.3-54 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Peppermint 3 mg - 60 min

Time point (min)	Statistics	PSWL60	ZP360	Change in PSWL60	Change in ZP360	Change in PSWL60 - Change in ZP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5565
	Mean (Std)	6.89 (13.43)	5.06 (7.56)	6.89 (13.43)	5.06 (7.56)	1.83 (12.97)	Signed Rank	0.5308
	Median (min;max)	3.5 (0;56)	3 (0;28)	3.5 (0;56)	3 (0;28)	0 (-28;39)		
	Q1, Q3 (IQR)	0 7 (7)	0 5 (5)	0 7 (7)	0 5 (5)	-1 4 (5)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1764
	Mean (Std)	12.67 (13.27)	8.72 (8.29)	12.67 (13.27)	8.72 (8.29)	3.94 (11.86)	Signed Rank	0.2570
	Median (min;max)	9.5 (0;45)	5 (0;23)	9.5 (0;45)	5 (0;23)	2 (-12;35)		
	Q1, Q3 (IQR)	3 16 (13)	2 20 (18)	3 16 (13)	2 20 (18)	-4 10 (14)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1731
	Mean (Std)	13.11 (11.63)	9 (8.4)	13.11 (11.63)	9 (8.4)	4.11 (12.27)	Signed Rank	0.2014
	Median (min;max)	10.5 (0;44)	5.5 (0;26)	10.5 (0;44)	5.5 (0;26)	2 (-12;44)		
	Q1, Q3 (IQR)	4 18 (14)	2 16 (14)	4 18 (14)	2 16 (14)	-2 5 (7)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5406
	Mean (Std)	10.39 (10.6)	8.78 (10.59)	10.39 (10.6)	8.78 (10.59)	1.61 (10.94)	Signed Rank	0.3660
	Median (min;max)	7 (0;34)	5 (0;38)	7 (0;34)	5 (0;38)	1 (-26;21)		
	Q1, Q3 (IQR)	3 13 (10)	0 14 (14)	3 13 (10)	0 14 (14)	-1 8 (9)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0432
	Mean (Std)	6.17 (8.04)	1.72 (4.04)	6.17 (8.04)	1.72 (4.04)	4.44 (8.63)	Signed Rank	0.0488
	Median (min;max)	1.5 (0;24)	0 (0;15)	1.5 (0;24)	0 (0;15)	0 (-9;24)		
	Q1, Q3 (IQR)	0 10 (10)	0 0 (0)	0 10 (10)	0 0 (0)	0 7 (7)		

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Table 14.3-55 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) - 60 min vs. ZYN® Spearmint 3 mg - 60 min

Time point (min)	Statistics	PSWL60	ZSP360	Change in PSWL60	Change in ZSP360	Change in PSWL60 - Change in ZSP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1204
	Mean (Std)	6.89 (13.43)	3.11 (6.43)	6.89 (13.43)	3.11 (6.43)	3.78 (9.8)	Signed Rank	0.1841
	Median (min;max)	3.5 (0;56)	0 (0;24)	3.5 (0;56)	0 (0;24)	0 (-10;32)		
	Q1, Q3 (IQR)	0 7 (7)	0 3 (3)	0 7 (7)	0 3 (3)	0 7 (7)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0154
	Mean (Std)	12.67 (13.27)	5.33 (6.95)	12.67 (13.27)	5.33 (6.95)	7.33 (11.55)	Signed Rank	0.0088
	Median (min;max)	9.5 (0;45)	2.5 (0;23)	9.5 (0;45)	2.5 (0;23)	4 (-9;33)		
	Q1, Q3 (IQR)	3 16 (13)	0 8 (8)	3 16 (13)	0 8 (8)	1 10 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0033
	Mean (Std)	13.11 (11.63)	5.67 (6.62)	13.11 (11.63)	5.67 (6.62)	7.44 (9.26)	Signed Rank	<.0001
	Median (min;max)	10.5 (0;44)	4 (0;21)	10.5 (0;44)	4 (0;21)	4 (0;34)		
	Q1, Q3 (IQR)	4 18 (14)	0 9 (9)	4 18 (14)	0 9 (9)	2 9 (7)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0931
	Mean (Std)	10.39 (10.6)	6.17 (6.69)	10.39 (10.6)	6.17 (6.69)	4.22 (10.07)	Signed Rank	0.0350
	Median (min;max)	7 (0;34)	5.5 (0;21)	7 (0;34)	5.5 (0;21)	4 (-21;26)		
	Q1, Q3 (IQR)	3 13 (10)	0 9 (9)	3 13 (10)	0 9 (9)	0 7 (7)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0056
	Mean (Std)	6.17 (8.04)	1.17 (3.59)	6.17 (8.04)	1.17 (3.59)	5 (6.69)	Signed Rank	0.0039
	Median (min;max)	1.5 (0;24)	0 (0;15)	1.5 (0;24)	0 (0;15)	1.5 (0;21)		
	Q1, Q3 (IQR)	0 10 (10)	0 0 (0)	0 10 (10)	0 0 (0)	0 9 (9)		

SM17 01 Analysis of secondary endpoint - VAS, SAS program: sec endpoint vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-19T07:15:52

Table 14.3-56 Change in VAS (pairwise): ZYN[®] Smooth 3 mg - 15 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	ZS315	ZS3A15	Change in ZS315	Change in ZS3A15	Change in ZS315 - Change in ZS3A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8574
	Mean (Std)	4.89 (4.66)	5.28 (10.22)	4.89 (4.66)	5.28 (10.22)	-0.39 (9.04)	Signed Rank	0.4170
	Median (min;max)	4.5 (0;14)	1 (0;43)	4.5 (0;14)	1 (0;43)	0 (-30;12)		
	Q1, Q3 (IQR)	0 8 (8)	0 7 (7)	0 8 (8)	0 7 (7)	-1 5 (6)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9542
	Mean (Std)	11.06 (12.46)	11.22 (17.09)	11.06 (12.46)	11.22 (17.09)	-0.17 (12.14)	Signed Rank	0.5363
	Median (min;max)	5.5 (0;39)	3 (0;57)	5.5 (0;39)	3 (0;57)	1 (-31;18)		
	Q1, Q3 (IQR)	2 23 (21)	0 21 (21)	2 23 (21)	0 21 (21)	-2 4 (6)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8203
	Mean (Std)	12.56 (14.6)	11.94 (14.65)	12.56 (14.6)	11.94 (14.65)	0.61 (11.24)	Signed Rank	0.9022
	Median (min;max)	5.5 (0;40)	5 (0;45)	5.5 (0;40)	5 (0;45)	0 (-24;31)		
	Q1, Q3 (IQR)	1 30 (29)	1 21 (20)	1 30 (29)	1 21 (20)	-4 4 (8)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5704
	Mean (Std)	2.33 (4.67)	1.83 (6.14)	2.33 (4.67)	1.83 (6.14)	0.5 (3.67)	Signed Rank	0.4688
	Median (min;max)	0 (0;17)	0 (0;26)	0 (0;17)	0 (0;26)	0 (-9;11)		
	Q1, Q3 (IQR)	0 2 (2)	0 0 (0)	0 2 (2)	0 0 (0)	0 0 (0)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		

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Table 14.3-57 Change in VAS (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Smooth 3 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	ZS360	ZS3A60	Change in ZS360	Change in ZS3A60	Change in ZS360 - Change in ZS3A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8221
	Mean (Std)	5.06 (8.39)	5.56 (10.13)	5.06 (8.39)	5.56 (10.13)	-0.5 (9.29)	Signed Rank	1.0000
	Median (min;max)	0 (0;25)	0 (0;37)	0 (0;25)	0 (0;37)	0 (-26;18)		
	Q1, Q3 (IQR)	0 6 (6)	0 7 (7)	0 6 (6)	0 7 (7)	0 0 (0)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5162
	Mean (Std)	8.67 (12.07)	9.61 (13.51)	8.67 (12.07)	9.61 (13.51)	-0.94 (6.04)	Signed Rank	0.9131
	Median (min;max)	0.5 (0;36)	2 (0;39)	0.5 (0;36)	2 (0;39)	0 (-17;9)		
	Q1, Q3 (IQR)	0 18 (18)	0 19 (19)	0 18 (18)	0 19 (19)	-1 2 (3)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5959
	Mean (Std)	11.06 (12.31)	9.5 (14.31)	11.06 (12.31)	9.5 (14.31)	1.56 (12.21)	Signed Rank	0.5264
	Median (min;max)	7.5 (0;37)	3 (0;42)	7.5 (0;37)	3 (0;42)	0.5 (-30;31)		
	Q1, Q3 (IQR)	0 20 (20)	0 10 (10)	0 20 (20)	0 10 (10)	-3 6 (9)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7642
	Mean (Std)	7.5 (9.53)	8.17 (9.87)	7.5 (9.53)	8.17 (9.87)	-0.67 (9.28)	Signed Rank	0.6222
	Median (min;max)	4 (0;32)	4.5 (0;34)	4 (0;32)	4.5 (0;34)	0 (-20;20)		
	Q1, Q3 (IQR)	0 13 (13)	0 10 (10)	0 13 (13)	0 10 (10)	-5 2 (7)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8822
	Mean (Std)	2.39 (4.29)	2.67 (6.77)	2.39 (4.29)	2.67 (6.77)	-0.28 (7.84)	Signed Rank	0.8750
	Median (min;max)	0 (0;17)	0 (0;23)	0 (0;17)	0 (0;23)	0 (-19;17)		
	Q1, Q3 (IQR)	0 4 (4)	0 0 (0)	0 4 (4)	0 0 (0)	0 1 (1)		

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Table 14.3-58 Change in VAS (pairwise): ZYN[®] Smooth 6 mg - 15 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 15 min

Time point (min)	Statistics	Change in ZS615	ZS6A15	Change in ZS615	ZS6A15	Change in ZS615 - ZS6A15	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0370
	Mean (Std)	9.5 (14.13)	5.44 (8.41)	9.5 (14.13)	5.44 (8.41)	4.06 (7.6)	Signed Rank	0.0458
	Median (min;max)	4 (0;45)	2 (0;27)	4 (0;45)	2 (0;27)	1 (-3;25)		
	Q1, Q3 (IQR)	1 9 (8)	0 8 (8)	1 9 (8)	0 8 (8)	0 7 (7)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5330
	Mean (Std)	13.44 (18.98)	15.33 (22.2)	13.44 (18.98)	15.33 (22.2)	-1.89 (12.59)	Signed Rank	0.4594
	Median (min;max)	5.5 (0;56)	5 (0;76)	5.5 (0;56)	5 (0;76)	-1 (-30;27)		
	Q1, Q3 (IQR)	1 18 (17)	2 25 (23)	1 18 (17)	2 25 (23)	-3 1 (4)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5349
	Mean (Std)	14.28 (16.79)	12.39 (20.1)	14.28 (16.79)	12.39 (20.1)	1.89 (12.65)	Signed Rank	0.2363
	Median (min;max)	7 (0;55)	4 (0;81)	7 (0;55)	4 (0;81)	1 (-37;28)		
	Q1, Q3 (IQR)	4 20 (16)	0 20 (20)	4 20 (16)	0 20 (20)	0 7 (7)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3045
	Mean (Std)	4.39 (8.54)	2.83 (7.39)	4.39 (8.54)	2.83 (7.39)	1.56 (6.23)	Signed Rank	0.4180
	Median (min;max)	0 (0;27)	0 (0;24)	0 (0;27)	0 (0;24)	0 (-7;24)		
	Q1, Q3 (IQR)	0 4 (4)	0 0 (0)	0 4 (4)	0 0 (0)	0 2 (2)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2591
	Mean (Std)	0 (0)	4.33 (15.75)	0 (0)	4.33 (15.75)	-4.33 (15.75)	Signed Rank	0.2500
	Median (min;max)	0 (0;0)	0 (0;67)	0 (0;0)	0 (0;67)	0 (-67;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		

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Table 14.3-59 Change in VAS (pairwise): ZYN[®] Smooth 6 mg - 60 min vs. ZYN[®] Smooth 6 mg (alt. manu. proc.) - 60 min

Time point (min)	Statistics	ZS660	ZS6A60	Change in ZS660	Change in ZS6A60	Change in ZS660 - Change in ZS6A60	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7922
	Mean (Std)	6.22 (6.01)	7 (10.78)	6.22 (6.01)	7 (10.78)	-0.78 (12.33)	Signed Rank	0.6477
	Median (min;max)	7.5 (0;18)	2.5 (0;42)	7.5 (0;18)	2.5 (0;42)	0 (-42;15)		
	Q1, Q3 (IQR)	0 10 (10)	0 10 (10)	0 10 (10)	0 10 (10)	-1 6 (7)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9827
	Mean (Std)	13.33 (14.35)	13.28 (16.4)	13.33 (14.35)	13.28 (16.4)	0.06 (10.73)	Signed Rank	0.4626
	Median (min;max)	9 (0;49)	9 (0;64)	9 (0;49)	9 (0;64)	1 (-33;17)		
	Q1, Q3 (IQR)	3 19 (16)	3 13 (10)	3 19 (16)	3 13 (10)	-3 6 (9)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4299
	Mean (Std)	14.33 (12.56)	12.56 (16.94)	14.33 (12.56)	12.56 (16.94)	1.78 (9.33)	Signed Rank	0.1884
	Median (min;max)	10.5 (0;42)	6.5 (0;58)	10.5 (0;42)	6.5 (0;58)	3 (-23;15)		
	Q1, Q3 (IQR)	5 24 (19)	2 16 (14)	5 24 (19)	2 16 (14)	-1 9 (10)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.8403
	Mean (Std)	12.56 (12.51)	11.89 (14.57)	12.56 (12.51)	11.89 (14.57)	0.67 (13.83)	Signed Rank	0.8446
	Median (min;max)	9.5 (0;49)	6.5 (0;49)	9.5 (0;49)	6.5 (0;49)	0.5 (-24;34)		
	Q1, Q3 (IQR)	3 20 (17)	2 15 (13)	3 20 (17)	2 15 (13)	-6 7 (13)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2431
	Mean (Std)	7 (8.41)	4.44 (6.71)	7 (8.41)	4.44 (6.71)	2.56 (8.97)	Signed Rank	0.3142
	Median (min;max)	4 (0;24)	0.5 (0;24)	4 (0;24)	0.5 (0;24)	0 (-14;23)		
	Q1, Q3 (IQR)	0 12 (12)	0 7 (7)	0 12 (12)	0 7 (7)	-2 5 (7)		

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Table 14.3-60 Change in VAS (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Wintergreen 3 mg - 60 min

Time point (min)	Statistics	ZS360	SW360	Change in ZS360	Change in SW360	Change in ZS360 - Change in SW360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7388
	Mean (Std)	5.06 (8.39)	4.17 (9.43)	5.06 (8.39)	4.17 (9.43)	0.89 (11.12)	Signed Rank	0.5313
	Median (min;max)	0 (0;25)	0 (0;33)	0 (0;25)	0 (0;33)	0 (-33;23)		
	Q1, Q3 (IQR)	0 6 (6)	0 3 (3)	0 6 (6)	0 3 (3)	0 3 (3)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2897
	Mean (Std)	8.67 (12.07)	10.11 (14.25)	8.67 (12.07)	10.11 (14.25)	-1.44 (5.61)	Signed Rank	0.3625
	Median (min;max)	0.5 (0;36)	4 (0;52)	0.5 (0;36)	4 (0;52)	0 (-16;7)		
	Q1, Q3 (IQR)	0 18 (18)	0 19 (19)	0 18 (18)	0 19 (19)	-4 1 (5)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7957
	Mean (Std)	11.06 (12.31)	10.44 (13.33)	11.06 (12.31)	10.44 (13.33)	0.61 (9.86)	Signed Rank	0.7721
	Median (min;max)	7.5 (0;37)	5.5 (0;51)	7.5 (0;37)	5.5 (0;51)	1.5 (-21;20)		
	Q1, Q3 (IQR)	0 20 (20)	0 14 (14)	0 20 (20)	0 14 (14)	-6 6 (12)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.4447
	Mean (Std)	7.5 (9.53)	10.39 (15.49)	7.5 (9.53)	10.39 (15.49)	-2.89 (15.67)	Signed Rank	0.6095
	Median (min;max)	4 (0;32)	4.5 (0;47)	4 (0;32)	4.5 (0;47)	0 (-44;24)		
	Q1, Q3 (IQR)	0 13 (13)	0 9 (9)	0 13 (13)	0 9 (9)	-7 3 (10)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5655
	Mean (Std)	2.39 (4.29)	1.5 (4.83)	2.39 (4.29)	1.5 (4.83)	0.89 (6.43)	Signed Rank	0.3438
	Median (min;max)	0 (0;17)	0 (0;20)	0 (0;17)	0 (0;20)	0 (-18;17)		
	Q1, Q3 (IQR)	0 4 (4)	0 0 (0)	0 4 (4)	0 0 (0)	0 2 (2)		

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Table 14.3-61 Change in VAS (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Peppermint 3 mg - 60 min

Time point (min)	Statistics	ZS360	ZP360	Change in ZS360	Change in ZP360	Change in ZS360 - Change in ZP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	1.0000
	Mean (Std)	5.06 (8.39)	5.06 (7.56)	5.06 (8.39)	5.06 (7.56)	0 (9.6)	Signed Rank	0.8345
	Median (min;max)	0 (0;25)	3 (0;28)	0 (0;25)	3 (0;28)	0 (-28;19)		
	Q1, Q3 (IQR)	0 6 (6)	0 5 (5)	0 6 (6)	0 5 (5)	-3 1 (4)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.9818
	Mean (Std)	8.67 (12.07)	8.72 (8.29)	8.67 (12.07)	8.72 (8.29)	-0.06 (10.17)	Signed Rank	0.7093
	Median (min;max)	0.5 (0;36)	5 (0;23)	0.5 (0;36)	5 (0;23)	-1 (-20;25)		
	Q1, Q3 (IQR)	0 18 (18)	2 20 (18)	0 18 (18)	2 20 (18)	-4 3 (7)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5059
	Mean (Std)	11.06 (12.31)	9 (8.4)	11.06 (12.31)	9 (8.4)	2.06 (12.83)	Signed Rank	0.5578
	Median (min;max)	7.5 (0;37)	5.5 (0;26)	7.5 (0;37)	5.5 (0;26)	0 (-26;28)		
	Q1, Q3 (IQR)	0 20 (20)	2 16 (14)	0 20 (20)	2 16 (14)	-3 10 (13)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.7030
	Mean (Std)	7.5 (9.53)	8.78 (10.59)	7.5 (9.53)	8.78 (10.59)	-1.28 (13.98)	Signed Rank	0.9891
	Median (min;max)	4 (0;32)	5 (0;38)	4 (0;32)	5 (0;38)	0 (-38;20)		
	Q1, Q3 (IQR)	0 13 (13)	0 14 (14)	0 13 (13)	0 14 (14)	-5 3 (8)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.5740
	Mean (Std)	2.39 (4.29)	1.72 (4.04)	2.39 (4.29)	1.72 (4.04)	0.67 (4.93)	Signed Rank	0.9336
	Median (min;max)	0 (0;17)	0 (0;15)	0 (0;17)	0 (0;15)	0 (-7;17)		
	Q1, Q3 (IQR)	0 4 (4)	0 0 (0)	0 4 (4)	0 0 (0)	0 1 (1)		

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Table 14.3-62 Change in VAS (pairwise): ZYN[®] Smooth 3 mg - 60 min vs. ZYN[®] Spearmint 3 mg - 60 min

Time point (min)	Statistics	ZS360	ZSP360	Change in ZS360	Change in ZSP360	Change in ZS360 - Change in ZSP360	Statistical test	P-value
0	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	
	Mean (Std)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.2104
	Mean (Std)	5.06 (8.39)	3.11 (6.43)	5.06 (8.39)	3.11 (6.43)	1.94 (6.34)	Signed Rank	0.4336
	Median (min;max)	0 (0;25)	0 (0;24)	0 (0;25)	0 (0;24)	0 (-5;21)		
	Q1, Q3 (IQR)	0 6 (6)	0 3 (3)	0 6 (6)	0 3 (3)	-1 1 (2)		
10	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.1923
	Mean (Std)	8.67 (12.07)	5.33 (6.95)	8.67 (12.07)	5.33 (6.95)	3.33 (10.41)	Signed Rank	0.3535
	Median (min;max)	0.5 (0;36)	2.5 (0;23)	0.5 (0;36)	2.5 (0;23)	0 (-7;36)		
	Q1, Q3 (IQR)	0 18 (18)	0 8 (8)	0 18 (18)	0 8 (8)	-1 3 (4)		
15	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0634
	Mean (Std)	11.06 (12.31)	5.67 (6.62)	11.06 (12.31)	5.67 (6.62)	5.39 (11.51)	Signed Rank	0.0757
	Median (min;max)	7.5 (0;37)	4 (0;21)	7.5 (0;37)	4 (0;21)	1.5 (-9;30)		
	Q1, Q3 (IQR)	0 20 (20)	0 9 (9)	0 20 (20)	0 9 (9)	0 8 (8)		
30	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.3929
	Mean (Std)	7.5 (9.53)	6.17 (6.69)	7.5 (9.53)	6.17 (6.69)	1.33 (6.45)	Signed Rank	0.5303
	Median (min;max)	4 (0;32)	5.5 (0;21)	4 (0;32)	5.5 (0;21)	0 (-8;22)		
	Q1, Q3 (IQR)	0 13 (13)	0 9 (9)	0 13 (13)	0 9 (9)	-1 4 (5)		
60	n (nmiss)	18 (0)	18 (0)	18 (0)	18 (0)	18 (0)	Student's t	0.0141
	Mean (Std)	2.39 (4.29)	1.17 (3.59)	2.39 (4.29)	1.17 (3.59)	1.22 (1.9)	Signed Rank	0.0234
	Median (min;max)	0 (0;17)	0 (0;15)	0 (0;17)	0 (0;15)	0 (-1;5)		
	Q1, Q3 (IQR)	0 4 (4)	0 0 (0)	0 4 (4)	0 0 (0)	0 3 (3)		

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Table 14.3-63 Descriptive statistics of extracted flavor

Statistics	Flavor Compound	Wintergreen	Peppermint	Spearmint
n (nmiss)	carvone			18 (0)
Mean (Std)	carvone			0.36 (0.18)
Median (min;max)	carvone			0.34 (0.16;0.85)
Q1, Q3 (IQR)	carvone			0.22 0.39 (0.17)
n (nmiss)	menthol		18 (0)	18 (0)
Mean (Std)	menthol		0.22 (0.13)	0.08 (0.04)
Median (min;max)	menthol		0.21 (0.01;0.56)	0.06 (0.01;0.17)
Q1, Q3 (IQR)	menthol		0.15 0.29 (0.14)	0.05 0.1 (0.05)
n (nmiss)	menthone		18 (0)	
Mean (Std)	menthone		0.12 (0.06)	
Median (min;max)	menthone		0.11 (0.02;0.27)	
Q1, Q3 (IQR)	menthone		0.08 0.16 (0.08)	
n (nmiss)	methylsalicylate	18 (0)		
Mean (Std)	methylsalicylate	1.5 (0.68)		
Median (min;max)	methylsalicylate	1.25 (0.66;3.14)		
Q1, Q3 (IQR)	methylsalicylate	1.03 1.67 (0.64)		

SM17_01 Analysis of primary endpoint, SAS program: Primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-01-16T15:21:58

14.4 Adverse events

14.4.1 Displays of adverse events

Table 14.4-1 Serious treatment emergent AEs: Number of subjects with at least 1 AE, by treatment

Treatment	n
No AE	20

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

Table 14.4-2 Serious treatment emergent AEs: Number of subjects with at least 1 related AE, by treatment

Treatment	n	%
No AE	20	100.0%

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

Table 14.4-3 Baseline AEs: Number of AE

Treatment	Number of AE:s
Pre-treatment	1
Total	1

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

Table 14.4-4 Baseline AEs: Number of subjects with at least 1 AE

Treatment	n
No AE	19
Pre-treatment	1

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

Table 14.4-5 Baseline AEs: Subject unique AEs by MedDRA body class

Body System or Organ Class	Treatment	
	Pre-treatment	
	Number of subjects	% of subjects
Nervous system disorders	1	5.0%

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

Table 14.4-6 Baseline AEs: Subject unique AEs by MedDRA body class and PT

Body System or Organ Class	Dictionary-Derived Term	Treatment	
		Pre-treatment	
		Number of subjects	% of subjects
Nervous system disorders	Headache	1	5.0%

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

Table 14.4-7 Baseline AEs: Subject unique AEs by relation to study product and MedDRA body class and PT

Body System or Organ Class	Dictionary-Derived Term	Causality	Treatment	
			Pre-treatment	
			Number of subjects	% of subjects
Nervous system disorders	Headache	UNKNOWN	1	5.0%

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

Table 14.4-8 Serious baseline AEs: Number of subjects with at least 1 AE

Treatment	n
No AE	20

SM17_01 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-02-05T17:27:49

14.4.2 Listings of deaths, other serious adverse events and significant adverse events

Not applicable.

14.4.3 Narratives of deaths, other serious adverse events and significant adverse events

Not applicable.

14.4.4 Abnormal laboratory value listing (each subject)

Not applicable.

15 REFERENCE LIST

1. Fant RV, Henningfield JE, Nelson RA and Pickworth WB. Pharmacokinetics and pharmacodynamics of moist of snuff in humans. *Tob. Control* 1999;8;387-392.
2. Molander L and Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. *Eur J Clin Pharmacol.* 2001;56:813-819.
3. Lunell E and Curvall M. Nicotine Delivery and Subjective Effects of Swedish Portion Snus Compared With 4 mg Nicotine Polacrilex Chewing Gum. *Nicotine Tob Res* 2011;13(7): 573-578.
4. Henningfield JE, Radzius A, Cooper TM, Clayton RR. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *JAMA* 1990;264:1560-4.

16 APPENDICES

16.1 Study information

- 16.1.1 Protocol and protocol amendments
- 16.1.2 Sample CRF (unique pages only)
- 16.1.3 IEC approval including list of IEC members. Representative written subject information and sample consent form
- 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*)
- 16.1.5 Signatures of the Sponsor, Statistician and Principal Investigator
- 16.1.6 Listing of subjects receiving IP from specific batches, where more than one batch was used
- 16.1.7 Randomization scheme and codes (subject identification and treatment assigned)
- 16.1.8 Audit certificates (*if available*)
- 16.1.9 Documentation of statistical methods
- 16.1.10 Documentation of inter-laboratory standardization 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 Subject data listings

- 16.2.1 Discontinued subjects
 - Inclusion/exclusion exceptions
 - Disposition
 - Subject visits
 - Trial elements
 - Trial arms
 - Trial visits
- 16.2.2 Protocol deviations
 - Protocol deviations
- 16.2.3 Subjects excluded from the (efficacy) analysis
- 16.2.4 Demographic data and other baseline characteristics
 - Demographics
 - Medical history
 - Concomitant medications (duration)
 - Concomitant medications (indication)
- 16.2.5 Compliance and/or drug concentration data
 - Exposure
- 16.2.6 Individual clinical data (primary endpoints)
 - Vital signs
 - Questionnaires
- 16.2.7 AE listings
 - Adverse events

- 16.2.8 Listing of individual laboratory measurements by subject
 - Laboratory tests

16.3 Case report forms

- 16.3.1 CRFs for deaths, other SAEs and withdrawals for AE
- 16.3.2 Other CRFs submitted

Appendix 16 is provided as a separate document to the Clinical Study Report (CSR).