
Clinical Study Report

Investigational Product	ZYN®
Study code	SM 17-03
Report Version and date	Final v 2.0; 28JUN2019

Nicotine pharmacokinetics and subjective effects of 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) 20NOV2017 – 22JAN2018

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<p>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.</p>
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Summary of changes to the CSR v 1.0 dated 20DEC2018

The CSR v 1.0 has been updated as follows:

Ethnicity has been added to [Table 10.4-1](#) “Summary of demographic data and other baseline characteristics”

As a complement the original comparisons of pharmacokinetic (PK) parameters performed for all the 17 subjects evaluated in v 1.0 of the CSR (non-baseline adjusted data), additional analyses on non-baseline adjusted, as well as baseline adjusted, data have been performed on 12 subjects. Details are described in Section 9.8.2.

All new analyses are shown in Section 14 as follows:

- Section 14.3.1.2 Difference in AUC_{inf} (non-baseline adjusted data, N=12)
- Section 14.3.1.3 Difference in AUC_{inf} (baseline adjusted data, N=12)
- Section 14.3.2.3 Correlations AUC_{inf} and extracted nicotine (non-baseline adjusted data, N=12)
- Section 14.3.2.4 Correlations AUC_{inf} and extracted nicotine (baseline adjusted data, N=12)
- Section 14.3.2.7 Difference in pharmacokinetic parameters (non-baseline adjusted data, N=12)
- Section 14.3.2.8 Difference in pharmacokinetic parameters (baseline adjusted data, N=12)

All data, original and new, have been compared to identify any potential differences in the outcomes of the statistical analyses. The comparisons are shown below. In case there is a discrepancy in terms of statistical significance, the p-values are highlighted in bold. For a majority of comparisons, including the primary endpoint, there were no differences in the outcome of the result.

Primary endpoint

<i>Difference in AUC_{inf} (min*ng/mL)</i>				
Products	Statistical test	P-value original analysis	P-value (without baseline adjustment)	P-value (with baseline adjustment)
ZS3 - PSWL	Student's t	0.0055	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS3 – ZS6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0010	0.0005
ZS3 – ZSA3	Student's t	0.5498	0.0813	0.3118
	Signed Rank	0.9265	0.0522	0.2334
ZS3 – ZSA6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS6 - PSWL	Student's t	0.0102	0.0044	0.0035
	Signed Rank	0.0056	0.0024	0.0024
ZS6 – ZSA3	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS6 – ZSA6	Student's t	0.5293	0.2171	0.1424
	Signed Rank	0.4586	0.2661	0.1394
ZSA3 - PSWL	Student's t	0.0050	<.0001	<.0001
	Signed Rank	0.0005	0.0005	0.0005
ZSA3 – ZSA6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZSA3 – PSWL	Student's t	0.0014	0.0150	0.0232

<i>Difference in AUC_{inf} (min*ng/mL)</i>				
Products	Statistical test	P-value original analysis	P-value (without baseline adjustment)	P-value (with baseline adjustment)
	Signed Rank	0.0026	0.0210	0.0210

Secondary endpoints:

<i>Difference in AUC_{0-4} (min*ng/mL)</i>				
Products	Statistical test	P-value original analysis	P-value (without baseline adjustment)	P-value (with baseline adjustment)
ZS3 - PSWL	Student's t	0.0001	0.0002	<.0001
	Signed Rank	<.0001	0.0010	0.0010
ZS3 – ZS6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS3 – ZSA3	Student's t	0.4285	0.2707	0.6311
	Signed Rank	0.9265	0.1514	0.5186
ZS3 – ZSA6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS6 - PSWL	Student's t	0.0005	0.0017	0.0014
	Signed Rank	0.0007	0.0024	0.0024
ZS6 – ZSA3	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS6 – ZSA6	Student's t	0.1121	0.1189	0.0729
	Signed Rank	0.1594	0.0923	0.0161
ZSA3 - PSWL	Student's t	0.0010	<.0001	<.0001
	Signed Rank	0.0007	0.0005	0.0005
ZSA3 – ZSA6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZSA6-PSWL	Student's t	0.0012	0.0181	0.0280
	Signed Rank	0.0017	0.0210	0.0210

<i>Difference in AUC_{0-60} (min*ng/mL)</i>				
Products	Statistical test	P-value original analysis	P-value (without baseline adjustment)	P-value (with baseline adjustment)
ZS3 - PSWL	Student's t	0.0009	0.0045	0.0014
	Signed Rank	0.0013	0.0049	0.0015
ZS3 – ZS6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS3 – ZSA3	Student's t	0.5534	0.3071	0.5610
	Signed Rank	0.7819	0.3804	0.6221
ZS3 – ZSA6	Student's t	<.0001	0.0003	0.0003
	Signed Rank	<.0001	0.0005	0.0010
ZS6 - PSWL	Student's t	0.0001	0.0022	0.0018
	Signed Rank	0.0007	0.0068	0.0068
ZS6 – ZSA3	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0010	0.0005
ZS6 – ZSA6	Student's t	0.0190	0.0855	0.0492
	Signed Rank	0.0110	0.0771	0.0640
ZSA3 - PSWL	Student's t	0.0228	0.0014	0.0005
	Signed Rank	0.0267	0.0015	0.0010
ZSA3 – ZSA6	Student's t	0.0001	0.0003	0.0004
	Signed Rank	0.0002	0.0010	0.0010
ZSA6-PSWL	Student's t	0.0082	0.0323	0.0503
	Signed Rank	0.0110	0.0522	0.0771

<i>Difference in C_{max} (ng/mL)</i>				
Products	Statistical test	P-value original analysis	P-value (without baseline adjustment)	P-value (with baseline adjustment)
ZS3 - PSWL	Student's t	0.0001	0.0008	0.0004
	Signed Rank	<.0001	0.0010	0.0010
ZS3 – ZS6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS3 – ZSA3	Student's t	0.4346	0.5437	0.7231
	Signed Rank	0.6110	0.4229	0.7910
ZS3 – ZSA6	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS6 - PSWL	Student's t	<.0001	0.0017	0.0018
	Signed Rank	0.0004	0.0049	0.0049
ZS6 – ZSA3	Student's t	<.0001	<.0001	<.0001
	Signed Rank	<.0001	0.0005	0.0005
ZS6 – ZSA6	Student's t	0.0580	0.1875	0.1483
	Signed Rank	0.0493	0.1763	0.0923
ZSA3 - PSWL	Student's t	0.0012	0.0002	0.0001
	Signed Rank	0.0021	0.0010	0.0010
ZSA3 – ZSA6	Student's t	<.0001	0.0002	0.0003
	Signed Rank	<.0001	0.0005	0.0005
ZSA6-PSWL	Student's t	0.0012	0.0125	0.0162
	Signed Rank	0.0004	0.0122	0.0210

<i>Difference in terminal of half-life (min)</i>				
Products	Statistical test	P-value original analysis	P-value (without baseline adjustment)	P-value (with baseline adjustment)
ZS3 - PSWL	Student's t	0.3718	0.1647	0.1645
	Signed Rank	0.1594	0.1514	0.1514
ZS3 – ZS6	Student's t	0.1310	0.1077	0.1079
	Signed Rank	0.0638	0.0640	0.0640
ZS3 – ZSA3	Student's t	0.2864	0.0623	0.0622
	Signed Rank	0.4038	0.0640	0.0640
ZS3 – ZSA6	Student's t	0.3137	0.2283	0.2278
	Signed Rank	0.6112	0.3394	0.3394
ZS6 - PSWL	Student's t	0.2537	0.6948	0.6970
	Signed Rank	0.1594	0.4238	0.4238
ZS6 – ZSA3	Student's t	0.2017	0.6507	0.6520
	Signed Rank	0.1901	0.5693	0.5693
ZS6 – ZSA6	Student's t	0.1093	0.2404	0.2415
	Signed Rank	0.1202	0.2334	0.2661
ZSA3 - PSWL	Student's t	0.8814	0.9954	0.9971
	Signed Rank	0.5791	0.9097	0.9097
ZSA3 – ZSA6	Student's t	0.9081	0.5649	0.5655
	Signed Rank	0.7467	0.7334	0.7334
ZSA6-PSWL	Student's t	0.9923	0.6253	0.6250
	Signed Rank	0.7819	0.5693	0.5693

<i>Difference in T_{max} (ng/mL)</i>				
Products	Statistical test	P-value original analysis	P-value (without baseline adjustment)	P-value (with baseline adjustment)
ZS3 - PSWL	Student's t	0.3552	0.4708	0.3046
	Signed Rank	0.4668	0.6289	0.4531
ZS3 – ZS6	Student's t	0.3722	0.1447	0.1447
	Signed Rank	0.3125	0.1250	0.1250
ZS3 – ZSA3	Student's t	0.2484	0.6339	0.6339
	Signed Rank	0.2188	0.6250	0.6250
ZS3 – ZSA6	Student's t	0.1162	0.3743	0.3743
	Signed Rank	0.1797	0.5625	0.5625
ZS6 - PSWL	Student's t	0.0925	0.1664	0.0950
	Signed Rank	0.1094	0.1875	0.1875
ZS6 – ZSA3	Student's t	0.6013	0.7815	0.7815
	Signed Rank	0.8750	0.7500	0.7500
ZS6 – ZSA6	Student's t	0.0207	0.0857	0.0857
	Signed Rank	0.0156	0.1250	0.1250
ZSA3 - PSWL	Student's t	0.0556	0.1944	0.1095
	Signed Rank	0.1016	0.3438	0.5313
ZSA3 – ZSA6	Student's t	0.0147	0.0820	0.0820
	Signed Rank	0.0234	0.1875	0.1875
ZSA6-PSWL	Student's t	0.6580	1.0000	0.6846
	Signed Rank	0.6875	1.0000	1.0000

ZS3 = Zyn Smooth 3mg

ZS6 = Zyn Smooth 6mg

ZSA3 = Zyn Smooth 3mg (alt. manu. Proc.

ZSA6 = Zyn Smooth 6mg (alt. manu. Proc.)

PSWL = Swedish portion snus PSWL

[Appendix 16.1](#) has been updated to include a signature page for the CSR v 2.0.

[Appendix 16.2](#) has been updated to include a new listing of demographic data (including ethnicity) and additional listings of PK parameters.

[Appendix 16.3](#) and [16.4](#) have not been changed but have been updated to match CSR v 2.0.

[Appendix 16.5](#) including the bioanalytical report for the study has been added.

2 STUDY SYNOPSIS

Study Title Nicotine pharmacokinetics and subjective effects of 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 17-03	
Study period Date of first subject screened: 20 November 2017 Date of last subject completed: 22 January 2018	
Principle Investigator Jan Erik Berglund, MD, PhD CTC Clinical Trial Consultants AB	
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, 5-way cross-over, single dose administration.	
Objectives <u>Primary objective</u> To compare each subject's area under the plasma concentration time curve from time zero to infinity (AUC_{inf}) based on plasma concentrations of nicotine after administration of 1 single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of 1 single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine. <u>Secondary objectives</u> <ul style="list-style-type: none"> – To compare AUC_{60min}, maximum concentration (C_{max}), time to maximum concentration (T_{max}), AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch. – To compare the estimated in vivo extracted amount 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. – To compare pulse rate and subjective effects ("head buzz") after study product administration (as proxy for in vivo nicotine uptake). – Collection of adverse events (AEs) 	

Number of subjects

The planned number of subjects was 18.

In total, 39 subjects were screened and 18 subjects were enrolled into the study. Subjects were randomized to 1 of 4 treatment sequences (A-D). All subjects who were randomized to treatment sequence A (n=5), B (n=4) and D (n=4), respectively, completed the study. Of the 5 subjects randomized to treatment sequence C, 4 completed the study and 1 subject withdrew consent. For treatment sequences, see the section Methodology below.

Diagnosis and main eligibility criteria

Healthy subjects aged ≥ 19 years who had used tobacco-based snus for ≥ 1 year with a weekly consumption of 3 or more snus cans (brands with nicotine content $\leq 1\%$) or 2 or more cans (brands with nicotine content $> 1\%$) were considered eligible to participate in the study. Eligible subjects had a pulse increase of ≥ 10 beats/min with the first use of snus in the morning after overnight abstinence from any nicotine exposure.

Subjects who were pregnant or who had a history of hypertension or any cardiovascular disease were excluded. Subjects had to be abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each study day.

Methodology

Before study entry, subjects signed an informed consent form and subsequently underwent screening evaluations including smoking and snus use, medical history and pulse rate measurements before/after application of their usual brand of snus (Visit 1). The pre-snus application pulse rate assessment was made in abstinent condition from 8.00 p.m. the night before.

Subjects visited the clinic on separate days (Visit 2 to 6) for the 5 experimental sessions. The subjects were instructed to abstain from snus, cigarettes or other nicotine delivery products from 8.00 p.m. the evening before. All sessions were performed during the morning hours to facilitate abstinence. The subjects certified abstinence before each treatment was started.

The investigational products (IPs) 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 60 min and were instructed not to manipulate the pouch with the tongue or lips. The subjects were also instructed not to eat, drink, chew chewing gum or brush teeth from 30 min before application of treatment, during application of IPs and 30 min after the investigational product had been taken out. Each used pouch was collected and frozen (pending analysis of nicotine).

A telephone follow-up (Visit 7) was conducted 1 week after last dose.

The treatment sequences were:

- A: ZYN® Smooth 3 mg
 ZYN® Smooth 6 mg
 ZYN® Smooth 3 mg (alternative manufacturing process)
 ZYN® Smooth 6 mg (alternative manufacturing process)
 Swedish portion snus PSWL 1.0 g (8 mg/g)
- B: Swedish portion snus PSWL 1.0 g (8 mg/g)
 ZYN® Smooth 3 mg
 ZYN® Smooth 6 mg
 ZYN® Smooth 3 mg (alternative manufacturing process)
 ZYN® Smooth 6 mg (alternative manufacturing process)
- C: ZYN® Smooth 6 mg (alternative manufacturing process)
 Swedish portion snus PSWL 1.0 g (8 mg/g)
 ZYN® Smooth 3 mg
 ZYN® Smooth 6 mg
 ZYN® Smooth 3 mg (alternative manufacturing process)
- D: ZYN® Smooth 3 mg (alternative manufacturing process)
 ZYN® Smooth 6 mg (alternative manufacturing process)
 Swedish portion snus PSWL 1.0 g (8 mg/g)
 ZYN® Smooth 3 mg
 ZYN® Smooth 6 mg

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

Test products:

- 1= ZYN Smooth containing 3 mg nicotine per portion, powder batch/batch number: 91153
- 2= ZYN Smooth containing 6 mg nicotine per portion, powder batch/batch number: 91250
- 3= ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process), powder batch/batch number: MG170908
- 4= ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process), powder batch/batch number: MG170830

Reference product:

- 5= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g), powder batch/batch number: 11121K6013

All IPs were administered in pouches between the upper lip and the gum for 60 min.

Non-Investigational Products, dosage and mode of administration, batch number

Not applicable.

Duration of treatment

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 60 min.

Duration of subject's involvement in the study

Each subject participated in the study for 22 to 41 days. Subject 114 withdrew his consent after visit 2, i.e. after 6 days in the study. The subject returned for an end-of-study visit.

Efficacy assessments

Pharmacokinetic assessments - WinNonlin computer program (Certara Corp., USA) was used for pharmacokinetic calculations. Nicotine plasma concentrations were determined at preset time points, before (0) and at 5, 10, 15, 30 and 60 min, 1.5, 2, 4 and 6 h after administration of each product.

Vital signs – Pulse rate was measured at the following time points: before (0) and at 5, 10, 15, 30 and 60 min after administration of each product.

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 before (0) and at 5, 10, 15, 30 and 60 min after administration of each product.

Safety assessments

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).

Statistical methods

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 was 16 with a power of 80% and $\alpha=0.05$. The randomization was performed using Latin Squares approach.

AUC_{inf} based on plasma concentrations of nicotine after administration of 1 single dose of the non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, and that of 1 single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine was described using summary statistics and non-parametric Wilcoxon signed rank sum test for within subject difference.

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 reference product in all analyses. In addition, pairwise comparisons between the test products were performed.

The extracted dose of nicotine was analyzed using the Wilcoxon signed rank sum test and Student's t-test for within subject difference. The correlation between the AUC_{inf} and the total amount of nicotine extracted from the pouch was analyzed using Proc corr. in SAS. Graphs of extracted nicotine and AUC_{inf} were plotted for each treatment with a regression fit.

AUC_{60min} , C_{max} , T_{max} , AUC_{0-t} and terminal half-life of the non-tobacco-based nicotine pouch to that of a Swedish snus pouch were analyzed using Wilcoxon signed rank sum test for within subject difference.

Pulse rate and VAS scales for "head buzz" 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

There were statistically significant differences in mean AUC_{inf} between each of the 4 test products and the reference product Swedish portion snus PSWL 1.0 g (8 mg). The AUC_{inf} of the test products containing 3 mg nicotine was significantly lower compared to that of the reference product and the AUC_{inf} of the test products containing 6 mg was significantly higher.

The corresponding result was observed for the extracted amount of nicotine. The extracted amount of nicotine from the test products ZYN® 3 mg and ZYN® 3 mg (alternative manufacturing process) was significantly lower compared to that of the reference product. The extracted amount from ZYN® 6 mg and ZYN® 6 mg (alternative manufacturing process) was significantly higher compared to the reference product.

There were statistically significant differences in nicotine plasma concentrations between the 4 test products and the reference product at a majority of time points. The plasma concentrations from the test products containing 3 mg nicotine were significantly lower compared to those of the reference product. The plasma concentrations from the test products containing 6 mg were significantly higher compared to the reference product.

For the pharmacokinetic parameters there were statistically significant differences in AUC_{0-t} , AUC_{60min} and C_{max} between each of the test products and the reference product whereas no statistically significant differences were seen in terms of terminal half-life and T_{max} .

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. 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.

There were statistically significant differences in head buzz between each of the test products and the reference product at a majority of time points. The change in head buzz was larger in the reference group compared to each of the test products (3 mg and 6 mg) at all time points.

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 16 AEs was reported by 8 subjects during the study and 2 AEs (dry mouth) were judged to have a possible or probable relationship to treatment. There were no SAEs or discontinuations due to AEs during the study.

CONCLUSION

Despite a lower nicotine content, the non-tobacco-based ZYN® 6 mg products gave rise to significantly larger nicotine extraction and subsequent uptake of nicotine in the systemic blood circulation than did the conventional, tobacco-based snus (PSWL) 8 mg product. The larger nicotine exposure was not associated with a statistically significantly larger increase in pulse rate in the ZYN® 6 mg group compared to the PSWL group. Interestingly, the increase in head buzz was statistically significantly smaller in the ZYN® 6 mg group compared to the PSWL group.

Conventional, tobacco-based snus (PSWL) 8 mg gave rise to significantly larger nicotine extraction and subsequent uptake in the systemic blood circulation than did the non-tobacco-based ZYN® 3 mg products. The effect was not associated with a larger increase in pulse rate in the PSWL group compared to the ZYN® 3 mg group but was associated with a larger increase in head buzz in the PSWL group.

Both the test and the reference products 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
AUC	Area Under the plasma concentration time Curve
C _{max}	Maximum Concentration
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTC	Clinical Trial Consultants AB
CV	Coefficient of variation
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice
h	Hour
HIV	Human Immunodeficiency Virus
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
PK	Pharmacokinetics
PPS	Per Protocol Set
PSWL	Portion Snus White portion Large
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
sec	Second
SOC	System Organ Class
SOP	Standard Operating Procedures
TCA	Tricyclic Antidepressants
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
T _{max}	Time to maximum concentration
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 Clinical Trial Consultants (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 electronic Case Report Form (eCRF).

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 AB 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).

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 main aim of the present study was to document the in vivo extraction of nicotine from ZYN[®] pouches and the resulting uptake to the systemic blood circulation, measured as AUC_{inf}, based on plasma concentrations of nicotine, versus a conventional snus pouch. The extraction and plasma data were supplemented with assessments of subjective effects of “product strength” and pulse rate measurements, both of which constitute proxies for systemic nicotine uptake.

7.2 Investigational medicinal product

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.

7.3 Risk/benefit assessment

It may be considered problematic to expose research subjects to a novel nicotine delivery product the properties of which are not yet fully known. However, all research subjects were required to be daily snus users since at least 1 year (with an average or above snus consumption) so the participants were well acquainted with and used to the effects of nicotine. Preliminary data from the manufacturer (J. Lindholm, Sponsor's personal communication) indicate that the amount of nicotine extracted from the test articles was comparable to that from tobacco-based snus, despite the fact that the overall nicotine content and content of free nicotine in the ZYN[®] pouches, 3 and 6 mg, was lower than in conventional tobacco-based snus (8 mg). This suggested that adverse effects from the nicotine exposure from the test and reference articles were unlikely to occur among the research subjects.

Aside from the nicotine, all ingredients used in the test products are food-approved (similar to ingredients in conventional snus). The nicotine in ZYN[®] is of pharmaceutical grade, i.e. the same as the nicotine in nicotine replacement products (gum, lozenges, mouth spray etc.). ZYN[®] is currently commercially available on the U.S. and Swedish markets.

Prior to this study, no adverse effects have been reported associated with the use of ZYN[®] apart from effects likely to be related to the nicotine exposure (such as salivation, nausea, and dyspepsia).

Pregnant women or individuals with a history of hypertension or any cardiovascular disease, who may be particularly vulnerable to nicotine exposure, were excluded from participation.

The study did not involve invasive procedures, beside the collection of venous blood samples.

The potential adverse effects of the study procedures, which were likely to be minor and/or clinically insignificant, were from a research ethics perspective counterbalanced by the potential positive effects of the novel nicotine pouch as a reduced toxicity alternative in comparison with cigarettes or conventional snus among current tobacco users. As the nicotine delivery profile of a product was likely to be central to its acceptability among current tobacco users, it was reasonable to conduct formal clinical studies to assess this feature in more detail.

The subjects remained in the research clinic for 6 h after the administration of the IPs and were closely monitored by medical staff.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective

To compare each subject's area under the plasma concentration time curve from time zero to infinity (AUC_{inf}) based on plasma concentrations of nicotine after administration of 1 single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of 1 single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine

8.1.1 Primary endpoint

AUC_{inf} based on plasma concentrations of nicotine after administration of 1 single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of 1 single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine

8.2 Secondary objectives

- To compare AUC_{60min} , maximum concentration (C_{max}), time to maximum concentration (T_{max}), AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch
- To compare the estimated in vivo extracted amount 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
- To compare pulse rate and subjective effects ("head buzz") after study product administration (proxy for in vivo nicotine uptake)
- Collection of adverse events (AEs)

8.2.1 Secondary endpoints

- AUC_{60min} , C_{max} , T_{max} , AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch
- In vivo extracted amount of nicotine
- The correlation between the estimates of AUC_{inf} and the total amount of nicotine extracted from the ZYN[®] pouches
- Pulse rate and visual analog scale (VAS) for measurement of "head buzz" (head rush, "hit", feeling alert, overall "product strength"), using a 100-mm VAS anchored with "not at all" to "extremely" at present time points up to 60 min (predose, +5, +10, +15, +30, +60 min after each dose), respectively, after study product administration (proxy for systemic uptake)
- Collection of AEs

9 INVESTIGATIONAL PLAN

9.1 Overall study design and schedule of events

The study was conducted as an open, randomized, 5-way cross-over, single dose administration study. A total of 18 subjects were included.

The subjects included were healthy males and females aged ≥ 19 years who had used tobacco-based snus for >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 abstained from snus and all other nicotine containing products from 8.00 p.m. the night before each study day.

Before study entry, subjects signed an informed consent form and subsequently underwent screening evaluations including smoking and snus use, medical history and pulse measurements before/after application of their usual brand of snus (Visit 1). The pulse rate assessment was made in abstinent condition from 8.00 p.m. the night before. An increase in pulse of ≥ 10 beats/min in the morning before use of any nicotine containing product classified the subject as eligible for participation the study.

Subjects visited the clinic on separate days (Visits 2 to 6) for the 5 experimental sessions. The subjects were instructed to abstain from snus, cigarettes or other nicotine delivery products as from 8.00 p.m. the evening before. All sessions were performed during the morning hours to facilitate abstinence. The subjects certified abstinence before each treatment was started.

The IPs 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 60 min and were instructed not to manipulate the pouch with the tongue or lips. The subjects were instructed not to eat, drink, chew chewing gum or brush teeth from 30 min before application of treatment, during application of investigational products and 30 min after the IP had been taken out. Each used pouch was collected and frozen pending analyses of nicotine.

A telephone follow-up (Visit 7) was conducted 1 week after last dose.

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	Visit 2-6 ²	Visit 7
	Day -14 to -1	Day 1 followed by 1-14 day(s) of wash-out. Repeated for each dose time point	7 Days after last dose -3/+7 days
Informed consent	X		
Eligibility	X	X ⁸	
Demographics	X		
Prior and Concomitant medication	X	X	X
Medical history	X		
Urine pregnancy test ³	X		
HIV, Hepatitis B and C test	X		
Drug screen	X ⁴	X ⁴	
CO measurement	X	X	
Pulse rate	X ⁵	X ⁶	
Visual Analogue Scale		X ⁶	
IP administration		X	
Collection of pouches		X	
PK blood sampling		X ⁷	
Baseline symptoms	X	X ⁸	
AEs		X	X

HIV: Human immunodeficiency virus, CO: Carbon monoxide, PK: pharmacokinetics

1 Visit 1 could be performed during 2 days.

2 See Detailed schedule of events for details, see Section 12.2 in the study protocol ([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 IPs

7 Before and 5, 10, 15, 30, 60, 90, 120, 240 and 360 min after application of the IPs

8 Only prior to dose administration on visit 2.

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 are 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. It was thus intended to extend those observations by comparing a nicotine non-tobacco-based nicotine pouch (ZYN[®]) with Swedish snus, PSWL 1.0 g (8 mg nicotine/g).

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 18 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. Smoker, defined as "smoking during the last 24 h according to self-report and CO in exhaled air >10 ppm at clinical visits".
2. A history or presence of diagnosed hypertension or any cardiovascular disease.
3. 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.
4. Any surgical or medical condition, which, in the judgment of the clinical investigator, might interfere with the absorption, distribution, metabolism or excretion of the investigational product.
5. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
6. Pregnancy or planning to get pregnant during the study.
7. Positive screen for drugs of abuse at screening or on admission to the unit prior to administration of the IP.
8. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and HIV.

9. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse.
10. Use of any prescribed or non-prescribed medication including antacids, analgesics and herbal remedies within 2 weeks prior to the first administration of IP, except occasional intake of paracetamol (maximum 2 000 mg/day; and not exceeding 3000 mg/week), at the discretion of the Investigator.
11. Plasma donation within 1 month of Screening or any blood donation/blood loss >450 mL during the 3 months prior to Screening.
12. Investigator considered the subject unlikely to comply with study procedures, restrictions and requirements.

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 study day.
2. Subjects were to abstain from smoking the last 24 before each study day.
3. The subjects were not allowed to eat or drink or use any other mouth related procedure (e.g. tooth brushing) 30 min before dose administration, during application of IPs and 30 min after the IP had been taken out ([Henningfield JE et al 1990](#)).
4. Other therapy considered necessary for the subject's welfare was given at the discretion of the Investigator. All such therapy was recorded in the eCRF.
5. The female volunteers were expected to be sexually abstinent or use contraceptives to prevent pregnancy during the study period.
6. Consumption of grapefruit and/or grapefruit containing products was not allowed 1 week before IP dosing until last PK day.
7. Xanthine or taurine containing products/beverages, e.g. Redbull, was not allowed during the study.
8. Abstain from drugs of abuse from Screening to Follow-up visit.
9. The subjects were not allowed to donate blood or plasma during the study until 3 months after the Follow-up Visit.
10. 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 eCRFs were completed as far as possible.

9.3.6.1 Subject replacement

Subjects who were prematurely withdrawn from the study for any reason were not replaced.

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 products

Test products:

1=ZYN Smooth containing 3 mg nicotine per portion, powder batch/batch number: 91153

2=ZYN Smooth containing 6 mg nicotine per portion, powder batch/batch number: 91250

3=ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process), powder batch/batch number: MG170908

4=ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process), powder batch/batch number: MG170830

Reference product:

5=Swedish portion snus PSWL 1.0 g (8 mg nicotine/g), powder batch/batch number: 11121K6013

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	1	2	3	4
ZYN® Smooth 6 mg	2	3	4	5
ZYN® Smooth 3 mg (alt. manu. proc.)	3	4	5	1
ZYN® Smooth 6 mg (alt. manu. proc.)	4	5	1	2
Swedish portion snus PSWL 1.0 g (8 mg)	5	1	2	3

SM17_03 treatment definitions, SAS program: treatment_definitions.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:12:04

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 *HIV and Hepatitis B/C*

Subjects were tested for HIV and hepatitis B/C prior to inclusion into the study in order to protect personnel handling the blood samples.

9.5.1.5 *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).

9.5.1.6 *Pregnancy urine test*

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

9.5.1.7 *Carbon monoxide test*

Measurement of CO in exhaled air was performed at visits to the clinic.

9.5.1.8 *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 eCRF. 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 eCRF.

9.5.1.9 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 Pharmacokinetic assessments

Nicotine plasma concentrations were determined at preset time points, before (0) and 5, 10, 15, 30 and 60 min, and 1.5, 2, 4 and 6 h after administration. Frozen plasma samples collected for nicotine determinations were shipped to a certified contract laboratory. The analysis of the plasma samples was performed by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay at ABS Laboratories Ltd, UK. To quantify nicotine, a multilevel calibration at eight concentrations were performed over a range of 0 to 50 ng/mL. The calibration line was fitted by means of linear regression weighted by $1/\text{concentration}^2$. The samples were assayed once.

Incurred sample reproducibility was performed according to the European Medicines Agency (EMA) and Food and Drug Administration (FDA) guidelines so that 10% of the analyzed study samples up to 1000 were reanalyzed and then 5% of the number above 1000. The analysis batch acceptance criteria were: The calibration standards must have a back-calculated accuracy within $100 \pm 15\%$, except at the lower limit of quantification (LLOQ) where it had to be within $100 \pm 20\%$. The standard curve was constructed from at least 3 quarters (i.e. 12) of the calibration standards, excluding the zero concentration calibration standards. Duplicate quality control samples at low, medium and high concentrations were included in each analysis batch. The accuracy of at least two thirds of the quality control samples were within $100 \pm 15\%$. Half of the quality control samples at each concentration were within $100 \pm 15\%$. At least half of the blank samples with internal standard and half of the blank samples without internal standard, placed immediately before the calibration standards, were free of interference.

Overall two thirds of the total number of blank samples were free of interference. Interference was defined as a detectable response, at the retention time of the analyte, greater than 20% of the mean response of the lowest concentration standards. WinNonlin computer program (Certara Corp., USA) was used for PK calculations. Main variables were AUC_{inf} , C_{max} and T_{max} .

9.5.2.2 Visual Analogue Scale and vital signs

Head buzz (head rush, "hit", feeling alert, overall "product strength") was measured 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). VAS assessment was performed with a VAS-ruler. Pulse rate was measured using an automatic device in sitting position after 10 min of rest.

9.5.2.3 *Collection and analysis of pouches*

Pouches for the determination of nicotine after administration of the IP were collected after 60 min. The following time window applied for the pouch sampling:

- ± 1 min

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

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

9.5.3 **Adverse events**

Collection of baseline events started after the subject signed the ICF and continued until the first administration of IP. Collection of AEs started with administration of the IP 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 study ended. In addition, all SAEs 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 study was over. Such events were followed until they were resolved or until the Investigator assessed them as "chronic" or "stable".

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

For detailed definition and reporting procedures, see Section 12.6 in the CSP ([Appendix 16.1.1](#) to this report).

9.5.4 **Appropriateness of measurements**

Measurements of nicotine plasma concentration, 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.

An eCRF (Viedoc™) 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 100% SDV were performed on 5 subjects, randomly chosen.

All eCRFs 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), 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 4 test products were compared to the reference product in all analyses.

9.7.2 Determination of sample size

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 was 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 endpoints*

AUC_{inf} based on plasma concentrations of nicotine after administration of 1 single dose of the non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of 1 single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine was described using summary statistics and non-parametric Wilcoxon signed rank sum test for within subject difference.

9.7.6 *Analysis of secondary endpoints*

The mean \pm SD extracted amount 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 for within subject difference. The correlation between the AUC_{inf} and the total amount of nicotine extracted from the pouch were analyzed using Proc corr. in SAS.

Graphs of extracted nicotine and AUC_{inf} were plotted for each treatment with a regression fit.

The mean \pm SD of AUC_{inf} based on plasma concentrations of nicotine after administration of each pouch were calculated. AUC_{60min}, C_{max}, T_{max}, AUC_{0-t} and terminal half-life were also calculated.

AUC_{60min}, C_{max}, T_{max}, AUC_{0-t} and terminal half-life of the non-tobacco-based nicotine pouch to that of a Swedish snus pouch were described using summary statistics and analyzed using Wilcoxon signed rank sum test for within subject difference.

Pulse rate and VAS for measure of subjective "head buzz" (head rush, "hit", feeling alert, overall "product strength"), were summarized by treatment and period using descriptive statistics. Pulse rate and VAS scales for "head buzz" were analyzed using the Wilcoxon signed rank sum test and Student's t-test for within subject difference.

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 System Organ Class (SOC) and preferred term (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*

All p-values shown in the report are unadjusted, i.e. no correction due to multiple testing.

9.7.7.5 *Examination of subgroups*

No subgroup analyses were performed.

9.8 Changes in the conduct of the study or planned analyses

9.8.1 Changes not described in a formal protocol amendment

The protocol was updated once during the study (protocol version 1.1 05FEB2018) since the standard curve for the LC-MS/MS analysis of nicotine levels was replaced with a standard curve with the same number of measuring points but covering a lower concentration range (previous: 0 to 100 ng/mL, new: 0 to 50 ng/mL). The change was considered an administrative change.

Data on length and weight were collected from the recruitment database for body surface calculations, which were not planned for in the CSP but were described in the SAP (see Section 9.8.2).

9.8.2 Changes in the planned statistical analyses

The following analyses were not described in the CSP:

- Graphs of AUC_{inf} versus extracted nicotine and extracted nicotine divided by body surface, respectively, plotted for each treatment with a regression fit
- Pairwise comparisons between the test products
- Analysis of nicotine plasma concentration (comparisons between test products and the reference product and pairwise comparisons between the test products)
- Analysis of the rate of extraction of the dose of nicotine (comparisons between test products and the reference product and pairwise comparisons between the test products)

The PPS, rather than the FAS, was used in the analysis of the primary, secondary and safety variables. For details on subjects included in the analysis sets, refer to Section [10.3](#).

As a complement the original comparisons of pharmacokinetic (PK) parameters performed for all the 17 subjects evaluated in v 1.0 of the CSR (non-baseline adjusted data), additional analyses on non-baseline adjusted, as well as baseline adjusted, data have been performed on 12 subjects using the criteria outlined below.

Plasma concentrations below the quantification limit (0.5 ng/mL) were set to 0 before T_{\max} and to missing thereafter. The area under the plasma concentration versus time curve were calculated according to the linear up- log down method. The elimination constant (λ_Z) was calculated and the applied threshold for acceptance of regression was $R^2 \geq 0.85$, the threshold for % residual AUC $\leq 30\%$ and the threshold for half-life span was ≥ 1.0 . Subjects not fulfilling all 3 acceptance criteria were excluded from the analyses. The following subjects did not qualify.

Non-baseline adjusted data:

Subject 102 was not qualified according to the λ_Z acceptance criteria for all elements. 5/5 elements did not fulfill the threshold for % residual AUC $\leq 30\%$ and 3/5 did not fulfill the threshold for half-life span ≥ 1.0 (viz. Swedish portion snus PSWL 1.0g (8mg), ZYN[®] Smooth 3 mg (alt. manu. proc) and ZYN[®] Smooth 6 mg (alt. manu. proc)).

Subject 106 was not qualified according to the λ_Z acceptance criteria for all elements. 1/5 elements did not fulfill the criteria for acceptance of regression $R^2 \geq 0.85$ (viz. ZYN[®] Smooth 3 mg).

Subject 108 was not qualified according to the λ_Z acceptance criteria for all elements. 1/5 elements did not fulfill the threshold for % residual AUC $\leq 30\%$ (viz. Swedish portion snus PSWL 1.0g (8 mg)).

Subject 110 was not qualified according to the λ_Z acceptance criteria for all elements. 1/5 elements did not fulfill the threshold for % residual AUC $\leq 30\%$ (viz. ZYN[®] Smooth 3 mg) and 1/5 did not fulfill the threshold for half-life span ≥ 1.0 (viz. ZYN[®] Smooth 3 mg) and 1/5 elements did not fulfill the criteria for acceptance of regression $R^2 \geq 0.85$ (viz. ZYN[®] Smooth 3 mg).

Subject 113 was not qualified according to the λ_Z acceptance criteria for all elements. 1/5 elements did not fulfill the threshold for % residual AUC $\leq 30\%$ (viz. ZYN[®] Smooth 6 mg (alt. manu. proc)).

Baseline adjusted data:

Subject 102 was not qualified according to the λ_Z acceptance criteria for all elements. 5/5 elements did not fulfill the threshold for % residual AUC $\leq 30\%$ and 3/5 did not fulfill the threshold for half-life span ≥ 1.0 (viz. Swedish portion snus PSWL 1.0g (8mg), ZYN[®] Smooth 3 mg (alt. manu. proc) and ZYN[®] Smooth 6 mg (alt. manu. proc)).

Subject 108 was not qualified according to the λ_Z acceptance criteria for all elements. 1/5 elements did not fulfill the threshold for % residual AUC $\leq 30\%$ (viz. Swedish portion snus PSWL 1.0g (8 mg)).

Subject 110 was not qualified according to the λ_Z acceptance criteria for all elements. 1/5 elements did not fulfill the threshold for % residual AUC $\leq 30\%$ (viz. ZYN[®] Smooth 3 mg) and 1/5 did not fulfill the threshold for half-life span ≥ 1.0 (viz. ZYN[®] Smooth 3 mg) and 1/5 elements did not fulfill the criteria for acceptance of regression $R^2 \geq 0.85$ (viz. ZYN[®] Smooth 3 mg).

Consequently, 12 of 17 subjects were analysed in terms of comparisons of PK parameters and correlations between AUC_{inf} and extracted nicotine.

10 STUDY SUBJECTS

10.1 Disposition of subjects

10.1.1 Number of subjects

In total, 39 subjects were screened and 18 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 screened on 20 November 2017, the first dose was administered on 24 November 2017 and the last subject completed the study on 22 January 2018.

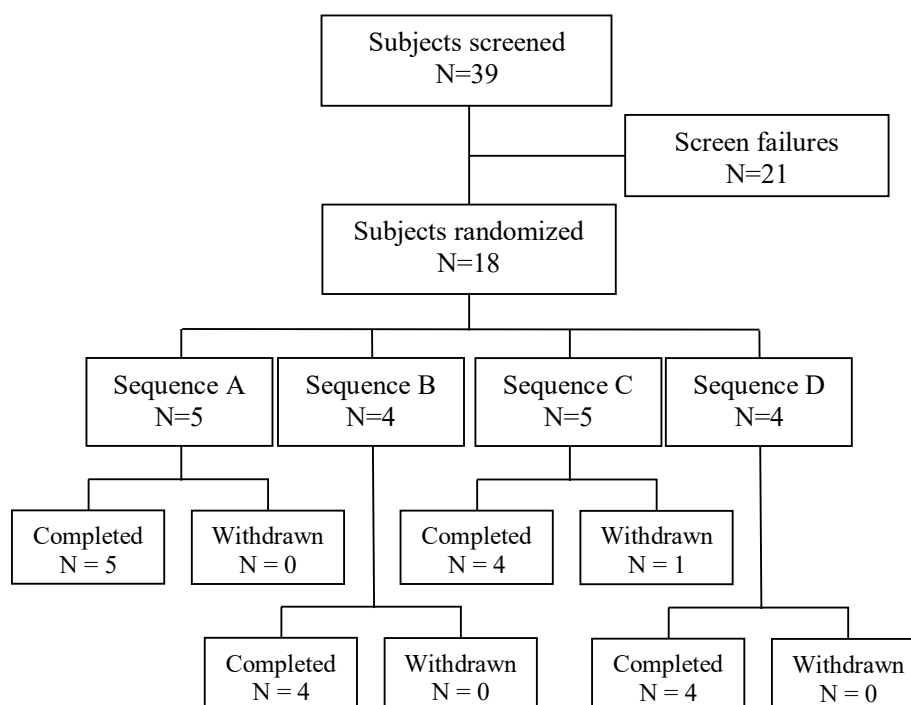
Subjects were randomized to 1 of 4 treatment sequences (A-D). All subjects who were randomized to treatment sequence A (5 subjects), B (5 subjects) and D (4 subjects), respectively, completed the study. Of the 5 subjects randomized to treatment sequence C, 4 subjects completed the study and 1 subject withdrew his consent and ended the study after visit 2. The disposition of subjects is shown in Table 10.1-2. 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 Appendix 16.2.1.

Table 10.1-1 Screen failures

Reason for non-inclusion	Number of subjects
Screening failure	8
Withdrawal of consent	9
Other, lost contact	4
Total number of screen failures	21

SM17_03 screen failures, SAS program: screen_failures.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-04-23T16:14:03

Table 10.1-2 Disposition of subjects



10.1.2 Study discontinuations

Subject 114, who was randomized to treatment sequence C, withdrew his consent and ended the study after visit 2, i.e. after treatment with ZYN® Smooth 6 mg (alternative manufacturing process), see [Appendix 16.2.1](#). The subject returned for an end-of-study visit.

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. A listing of all protocol deviations is presented as [Appendix 16.2.2](#).

10.3 Data sets analyzed

Eighteen (18) subjects were included in FAS and 17 subjects were included in PPS (Table 10.3-1). Subject 114 was excluded from the PPS due to withdrawal of consent ([Appendix 16.2.3](#)).

Table 10.3-1 Subjects included in the analysis sets

Unique Subject Identifier	FAS population (Y/N)	PPS population (Y/N)	Comment
SM17_03-101	Y	Y	
SM17_03-102	Y	Y	
SM17_03-103	Y	Y	
SM17_03-104	Y	Y	
SM17_03-105	Y	Y	

Unique Subject Identifier	FAS population (Y/N)	PPS population (Y/N)	Comment
SM17_03-106	Y	Y	
SM17_03-107	Y	Y	
SM17_03-108	Y	Y	
SM17_03-109	Y	Y	
SM17_03-110	Y	Y	
SM17_03-111	Y	Y	
SM17_03-112	Y	Y	
SM17_03-113	Y	Y	
SM17_03-114	Y	N	Withdrawal of consent
SM17_03-115	Y	Y	
SM17_03-116	Y	Y	
SM17_03-117	Y	Y	
SM17_03-118	Y	Y	

SM17_03 study populations, SAS program: population_flags.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:23:11

The plasma levels for Subject 102 was significantly higher than the average level for the others, see [Figure 14.3-1](#) to [Figure 14.3-5](#) (Section 14.3.2). The values were therefore reassessed but without detecting any errors behind and therefore this outlier was kept in the datasets.

10.3.1 Use of analysis sets

Since the PPS comprised 17 of 18 subjects and since Subject 114, who was excluded from the FAS, only received 1 dose of IP, all statistical analyses were performed using the PPS.

10.4 Demographics and other baseline characteristics

A total of 18 subjects (17 white, and 1 of Asian descent), 3 females and 15 males, were included in the study. The subjects had a mean (\pm SD) age of 37 ± 13 years and a mean pulse rate of 70 ± 8 beats/min at screening. All female subjects had a negative pregnancy test at screening. Demographic data for all subjects are summarized by treatment sequence in Table 10.4-1 below. For definitions of the treatment sequences, refer to [Table 9.4-1](#) in Section 9.4.2. Four (4) subjects had a medical history, but of no clinical significance, at the screening visit.

Individual subject demographic data, medical history and concomitant medications for all randomized subjects 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=4)	Treatment Sequence C (N=5)	Treatment Sequence D (N=4)	Total (N=18)
Age (years)	n/nmiss	5/0	4/0	5/0	4/0	18/0
	Mean (SD)	36.8 (11.9)	38.8 (20.4)	40 (11.5)	29.8 (7.04)	36.6 (12.7)
	Median (Min, Max)	37 (23, 53)	33 (22, 67)	40 (24, 54)	27.5 (24, 40)	36 (22, 67)
Gender	Female			1 (20%)	2 (50%)	3 (17%)
	Male	5 (100%)	4 (100%)	4 (80%)	2 (50%)	15 (83%)

		Treatment Sequence A (N=5)	Treatment Sequence B (N=4)	Treatment Sequence C (N=5)	Treatment Sequence D (N=4)	Total (N=18)
Race	Asian			1 (20%)		1 (6%)
	White	5 (100%)	4 (100%)	4 (80%)	4 (100%)	17 (94%)
Ethnicity	Not Hispanic	5 (100%)	4 (100%)	5 (100%)	4 (100%)	18 (100%)
Pulse (beats/min)	n/nmiss	5/0	4/0	5/0	4/0	18/0
	Mean (SD)	71.6 (8.05)	66.8 (6.6)	70.6 (9.58)	69 (9.56)	69.7 (8.01)
	Median (Min, Max)	72 (60, 80)	67 (59, 74)	73 (54, 78)	70.5 (56, 79)	71.5 (54, 80)
Pregnant at screening	Negative			1 (20%)	2 (50%)	3 (17%)
	Not Done	5 (100%)	4 (100%)	4 (80%)	2 (50%)	15 (83%)

SM17_03 summarized demographics data, SAS program: summary_demographics.sas. Run by: Lars Norberg, lars.norberg@ctc-ab.se 2019-06-25T09:12:14

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 60 min:

- 17 subjects received 2 single doses containing 3 mg nicotine, 2 single doses containing 6 mg nicotine and 1 single dose containing 8 mg nicotine
- 1 subject received 1 single dose containing 6 mg nicotine and thereafter withdrew from the study

Individual plasma concentration data are presented in [Appendix 16.2.5](#).

11.2 Evaluation of primary endpoint

11.2.1 AUC_{inf}

11.2.1.1 Comparison between test and reference products AUC_{inf}

There were statistically significant differences in mean AUC_{inf} between each of the 4 test products and the reference product Swedish portion snus PSWL 1.0 g (8 mg), see [Table 11.2-1](#) to [Table 11.2-4](#).

The mean AUC_{inf} of the test products containing 3 mg nicotine was significantly lower compared to that of the reference product. The AUC_{inf} for the test products containing 6 mg was significantly higher compared to the reference product.

Summary statistics of AUC_{inf} are presented in [Table 11.3-10](#) (Section [11.3.5](#)).

Table 11.2-1 *Difference in AUC_{inf} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg*

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0055
Mean (Std)	2793.14 (1883.68)	1906.77 (911.35)	886.37 (1138.82)	Signed Rank	<.0001
Median (min;max)	2326.7 (1421.49;9702.29)	1687.57 (835.27;4643)	661.87 (-7.68;5059.28)		
Q1, Q3 (IQR)	1891.29 2888.08 (996.79)	1374.18 2297.52 (923.34)	383.8 965.77 (581.97)		

SM17_03 Analysis of secondary endpoint - AUC_{inf} , SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 11.2-2 *Difference in AUC_{inf} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)*

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0050
Mean (Std)	2793.14 (1883.68)	1979.21 (1168.37)	813.94 (1031.47)	Signed Rank	0.0005
Median (min;max)	2326.7 (1421.49;9702.29)	1610.05 (449.58;5401.61)	571.75 (-670.92;4300.68)		
Q1, Q3 (IQR)	1891.29 2888.08 (996.79)	1321.68 2260.9 (939.22)	371.82 1091.94 (720.12)		

SM17_03 Analysis of secondary endpoint - AUC_{inf} , SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 11.2-3 *Difference in AUC_{inf} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg*

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0102
Mean (Std)	2793.14 (1883.68)	3581.26 (1541.27)	-788.12 (1116.6)	Signed Rank	0.0056
Median (min;max)	2326.7 (1421.49;9702.29)	3329.25 (1281.45;7556.81)	-957.67 (-2573.53;2145.48)		
Q1, Q3 (IQR)	1891.29 2888.08 (996.79)	2753.12 4476.15 (1723.03)	-1331.63 -563.76 (767.87)		

SM17_03 Analysis of secondary endpoint - AUC_{inf} , SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 11.2-4 *Difference in AUC_{inf} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)*

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0014
Mean (Std)	2793.14 (1883.68)	3453.7 (1792.41)	-660.56 (709.4)	Signed Rank	0.0026
Median (min;max)	2326.7 (1421.49;9702.29)	3202.21 (1334.97;9385.28)	-735.63 (-1706.2;612.46)		
Q1, Q3 (IQR)	1891.29 2888.08 (996.79)	2535.08 3964.3 (1429.22)	-1230.81 -47.12 (1183.69)		

SM17_03 Analysis of secondary endpoint - AUC_{inf} , SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

11.2.1.2 Pairwise comparison between the test products - AUC_{inf}

There were statistically significant differences in AUC_{inf} between:

- ZYN® Smooth 3 mg and 6 mg
- ZYN® Smooth 3 mg and 6 mg (alternative manufacturing process)
- ZYN® Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process)
- ZYN® Smooth 3 mg (alternative manufacturing process) and 6 mg

There were no statistically significant differences between:

- ZYN® Smooth 3 mg and 3 mg (alternative manufacturing process)
- ZYN® Smooth 6 mg and 6 mg (alternative manufacturing process)

Detailed information is presented in [Table 14.3-1](#) to [Table 14.3-6](#) (Section 14.3.1.1; non-baseline adjusted data, N=17). Additional comparisons are presented in [Table 14.3-7](#) to [Table 14.3-16](#) (Section 14.3.1.2; non-baseline adjusted data, N=12) and [Table 14.3-17](#) to [Table 14.3-26](#) (Section 14.3.1.3; baseline adjusted data, N=12).

11.3 Evaluation of secondary endpoints

11.3.1 Extracted amount of nicotine

Summary statistics of extracted amount of nicotine are presented in [Table 11.3-1](#). Individual subject data are provided in [Appendix 16.2.6](#).

Table 11.3-1 Extracted nicotine by treatment

Analyte (Unit)	Result Category	Treatment	N	Min	Max	Mean	Median	Std
Nicotine (mg)	Measured value	ZYN® Smooth 3 mg	17	0.604	2.65	1.51	1.45	0.603
		ZYN® Smooth 6 mg	17	1.7	5.84	3.77	3.73	1.17
		ZYN® Smooth 3 mg (alt. manu. proc.)	17	0.534	2.61	1.67	1.58	0.512
		ZYN® Smooth 6 mg (alt. manu. proc.)	17	1.4	5.09	3.24	3.53	1
		Swedish portion snus PSWL 1.0 g (8 mg)	17	1.25	3.62	2.41	2.45	0.735

SM17_03 LB tabulations, SAS program: safety_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:57:33

11.3.1.1 Comparison between test and reference products - extracted amount of nicotine

There were statistically significant differences in extracted amount of nicotine between each of the 4 test products and the reference product, see [Table 11.3-2](#) to [Table 11.3-5](#).

The extracted amount of nicotine from the test products containing 3 mg nicotine was significantly lower compared to that of the reference product. The extracted amount from the test products containing 6 mg was significantly higher compared to the reference product.

Table 11.3-2 *Difference in extracted nicotine (mg): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg*

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0001
Mean (Std)	2.41 (0.73)	1.51 (0.6)	0.9 (0.75)	Signed Rank	0.0004
Median (min;max)	2.45 (1.25;3.62)	1.45 (0.6;2.65)	1.12 (-0.5;2.05)		
Q1, Q3 (IQR)	1.82 2.95 (1.13)	0.99 1.82 (0.83)	0.43 1.5 (1.07)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 11.3-3 *Difference in extracted nicotine (mg): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg (alt. manu. proc.)*

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0003
Mean (Std)	2.41 (0.73)	1.67 (0.51)	0.74 (0.67)	Signed Rank	0.0009
Median (min;max)	2.45 (1.25;3.62)	1.58 (0.53;2.61)	0.79 (-0.39;1.57)		
Q1, Q3 (IQR)	1.82 2.95 (1.13)	1.51 2.1 (0.59)	0.2 1.38 (1.18)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 11.3-4 *Difference in extracted nicotine (mg): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg*

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	2.41 (0.73)	3.77 (1.17)	-1.35 (1)	Signed Rank	<.0001
Median (min;max)	2.45 (1.25;3.62)	3.73 (1.7;5.84)	-1.12 (-3.17;-0.03)		
Q1, Q3 (IQR)	1.82 2.95 (1.13)	3.11 4.88 (1.77)	-2.19 -0.55 (1.64)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 11.3-5 *Difference in extracted nicotine (mg): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg (alt. manu. proc.)*

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0054
Mean (Std)	2.41 (0.73)	3.24 (1)	-0.83 (1.07)	Signed Rank	0.0067
Median (min;max)	2.45 (1.25;3.62)	3.53 (1.4;5.09)	-0.53 (-2.94;0.7)		
Q1, Q3 (IQR)	1.82 2.95 (1.13)	2.64 3.75 (1.11)	-1.42 0.03 (1.45)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

11.3.1.2 Pairwise comparison between the test products – extracted amount of nicotine

There were statistically significant differences in extracted amount of nicotine between:

- ZYN[®] Smooth 3 mg and 6 mg
- ZYN[®] Smooth 3 mg and 6 mg (alternative manufacturing process)
- ZYN[®] Smooth 3 mg (alternative manufacturing process) and 6 mg
- ZYN[®] Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process)
- ZYN[®] Smooth 6 mg and 6 mg (alternative manufacturing process)

There was no statistically significant difference between:

- ZYN[®] Smooth 3 mg and 3 mg (alternative manufacturing process)

Detailed information is presented in [Table 14.3-27](#) to [Table 14.3-32](#) (Section 14.3.2).

11.3.1.3 Comparison between test and reference products – rate of extraction

There were statistically significant differences in rate of extraction between each of the 4 test products and the reference product, see [Table 11.3-6](#) to [Table 11.3-9](#). The rate of extraction for the test products was significantly higher compared to the reference product.

Table 11.3-6 Difference in rate of extraction (%): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0006
Mean (Std)	32.01 (9.57)	52.18 (20.98)	-20.17 (19.35)	Signed Rank	0.0003
Median (min;max)	32.28 (16.74;48.15)	50.2 (20.99;92.09)	-19.14 (-55.43;11.29)		
Q1, Q3 (IQR)	24.78 39.8 (15.02)	34.24 62.94 (28.7)	-27.18 -11.84 (15.34)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

Table 11.3-7 Difference in rate of extraction (%): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	32.01 (9.57)	59.63 (18.17)	-27.62 (15.93)	Signed Rank	<.0001
Median (min;max)	32.28 (16.74;48.15)	56.72 (18.95;93.08)	-25.66 (-56.42;9.45)		
Q1, Q3 (IQR)	24.78 39.8 (15.02)	54.11 75.21 (21.1)	-34.79 -19.05 (15.74)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

Table 11.3-8 Difference in rate of extraction (%): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	32.01 (9.57)	59.17 (18.04)	-27.15 (15.22)	Signed Rank	<.0001
Median (min;max)	32.28 (16.74;48.15)	59.41 (26.4;91.5)	-24.73 (-54.84;-5.12)		
Q1, Q3 (IQR)	24.78 39.8 (15.02)	49.19 75.98 (26.79)	-40 -16.79 (23.21)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

Table 11.3-9 Difference in rate of extraction (%): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	32.01 (9.57)	59.07 (18.2)	-27.06 (18.08)	Signed Rank	<.0001
Median (min;max)	32.28 (16.74;48.15)	63.6 (25.4;92.8)	-21.27 (-60.97;3)		
Q1, Q3 (IQR)	24.78 39.8 (15.02)	48.51 67.42 (18.91)	-36.22 -16.1 (20.12)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

11.3.1.4 Pairwise comparison between tests products – rate of extraction

There was a statistically significant difference in rate of extraction between:

- ZYN® Smooth 3 mg and 3 mg (alternative manufacturing process)

There were no statistically significant differences in rate of extraction between:

- ZYN® Smooth 3 mg and 6 mg
- ZYN® Smooth 3 mg and 6 mg (alternative manufacturing process)
- ZYN® Smooth 3 mg (alternative manufacturing process) and 6 mg
- ZYN® Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process)
- ZYN® Smooth 6 mg and 6 mg (alternative manufacturing process)

Detailed information is presented in Table 14.3-33 to Table 14.3-38 (Section 14.3.2).

11.3.2 Correlations - AUC_{inf} and extracted nicotine (non-baseline adjusted data, N=17)

Scatter plots of mean AUC_{inf} against extracted nicotine are presented for each treatment, respectively, together with a fitted linear regression line in Figure 14.3-1 to Figure 14.3-5 (Section 14.3.2.2). For all treatment groups, the regression lines seem to demonstrate a correlation. However, the correlations are judged to be relatively low based on the observed determination coefficient (r^2) values ranging from 0.072 to 0.30.

Scatter plots of AUC_{inf} against extracted nicotine divided by body surface (m^2) are presented for each treatment, respectively, together with a fitted linear regression line in Figure 14.3-6 to Figure 14.3-10 (Section 14.3.2.2). For all treatment groups, the regression lines seem to demonstrate a correlation. However, the correlations are judged to be relatively low based on the observed determination coefficient (r^2) values ranging from 0.14 to 0.45.

11.3.3 Correlations - AUC_{inf} and extracted nicotine (non-baseline adjusted and baseline adjusted data, N=12)

Additional plots are presented in Figure 14.3-11 to Figure 14.3-20 (Section 14.3.2.3; non-baseline adjusted data, N=12) and in Figure 14.3-21 to Figure 14.3-30 (Section 14.3.2.4; baseline adjusted data, N=12).

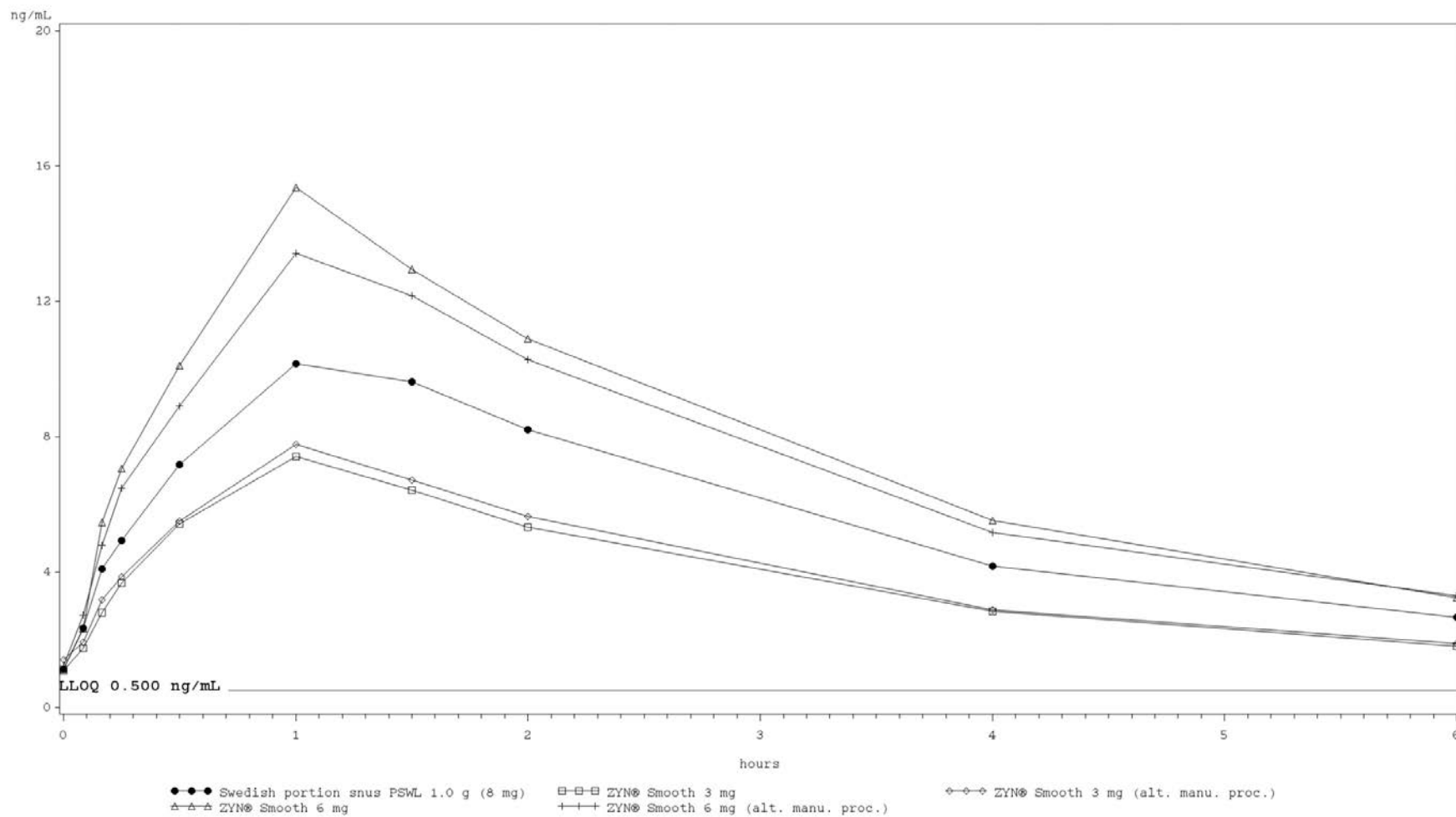
11.3.4 Nicotine plasma concentration

11.3.4.1 Comparison between test and reference products – nicotine plasma concentration

There were statistically significant differences between each of the 4 test products and the reference product, respectively, for a majority of time points from 10-15 min until 6 h after administration, see [Table 14.3-39](#) to [Table 14.3-42](#) (Section [14.3.2](#)). The nicotine plasma concentrations from the test products containing 3 mg nicotine were significantly lower compared to those of the reference product. The plasma concentrations from the test products containing 6 mg were significantly higher compared to the reference product.

Nicotine concentrations before (0) and 5, 10, 15, 30 and 60 min, and 1.5, 2, 4 and 6 h after administration are presented in [Figure 11.3-1](#) and summarized by treatment in [Table 14.3-49](#).

Figure 11.3-1 Mean plasma concentrations of nicotine (ng/mL)



Values <0.500 ng/mL (BLQ) imputed as 0.500 in graphs

SM17_03 PK conc mean figure, SAS program: pc_graphs_mean.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-05-09T14:39:17

11.3.4.2 Pairwise comparison between the test products – nicotine plasma concentration

There were statistically significant differences at a majority of time points from 5-10 min until 6 h after administration in nicotine plasma concentrations between:

- ZYN[®] Smooth 3 mg and 6 mg
- ZYN[®] Smooth 3 mg and 6 mg (alternative manufacturing process)
- ZYN[®] Smooth 3 mg (alternative manufacturing process) and 6 mg
- ZYN[®] Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process)

There were no statistically significant differences at any time point between:

- ZYN[®] Smooth 3 mg and 3 mg (alternative manufacturing process)
- ZYN[®] Smooth 6 mg and 6 mg (alternative manufacturing process) (except at 60 min after administration)

Detailed information is presented in [Table 14.3-43](#) to [Table 14.3-48](#) (Section 14.3.2).

11.3.5 Pharmacokinetic parameters

A summary of the PK parameters is given per treatment in Table 11.3-10. Individual subject data are provided in [Appendix 16.2.6](#).

Table 11.3-10 Pharmacokinetic parameters by treatment

Name of Treatment	Analyte (unit)	N	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN [®] Smooth 3 mg	AUC Infinity Obs (min*ng/mL)	17	835	1688	4640	1907	47.8	1746
	AUC from 0 to 60 min (min*ng/mL)	17	161	281.7	463	294.7	30.25	281.6
	AUC to Last Nonzero Conc (min*ng/mL)	17	639	1389	2960	1446	38.75	1355
	Half-Life Lambda z (min)	17	96.3	150.5	388	158.6	42.58	149.4
	Max Conc (ng/mL)	17	3.52	6.92	13.8	7.522	35.91	7.078
	Time of CMAX (min)	17	30	60	90	63.82	22.72	62.17
ZYN [®] Smooth 6 mg	AUC Infinity Obs (min*ng/mL)	17	1280	3329	7560	3581	43.04	3279
	AUC from 0 to 60 min (min*ng/mL)	17	257	522.9	935	568.9	28.99	546.3
	AUC to Last Nonzero Conc (min*ng/mL)	17	1140	2745	4800	2866	34.92	2683
	Half-Life Lambda z (min)	17	70.7	129.4	223	135.8	27.44	130.9
	Max Conc (ng/mL)	17	6.02	15	27.8	15.5	33.77	14.6
	Time of CMAX (min)	17	15	60	90	60.88	25.35	58
ZYN [®] Smooth 3 mg (alt. manu. proc.)	AUC Infinity Obs (min*ng/mL)	17	450	1610	5400	1979	59.03	1715
	AUC from 0 to 60 min (min*ng/mL)	17	104	266.2	595	307.3	43.59	280.6
	AUC to Last Nonzero Conc (min*ng/mL)	17	342	1420	2960	1505	43.93	1360
	Half-Life Lambda z (min)	17	89.8	131.2	279	143.1	32.67	137.2
	Max Conc (ng/mL)	17	2.17	7.48	12.1	7.828	36.5	7.248
	Time of CMAX (min)	17	30	60	90	58.29	22.08	56.69

Name of Treatment	Analyte (unit)	N	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN® Smooth 6 mg (alt. manu. proc.)	AUC Infinity Obs (min*ng/mL)	17	1330	3202	9390	3454	51.9	3132
	AUC from 0 to 60 min (min*ng/mL)	17	254	458	823	502.7	30.4	480.8
	AUC to Last Nonzero Conc (min*ng/mL)	17	1150	2668	5250	2658	37.28	2493
	Half-Life Lambda z (min)	17	83.7	137.2	268	143.6	29.79	138.4
	Max Conc (ng/mL)	17	7.21	12.8	24	13.86	33.45	13.19
	Time of CMAX (min)	17	60	60	91	70.71	20.96	69.34
Swedish portion snus PSWL 1.0 g (8 mg)	AUC Infinity Obs (min*ng/mL)	17	1420	2327	9700	2793	67.44	2484
	AUC from 0 to 60 min (min*ng/mL)	17	147	375.6	603	396.6	30.46	377.1
	AUC to Last Nonzero Conc (min*ng/mL)	17	1090	1942	5240	2114	44.24	1976
	Half-Life Lambda z (min)	17	98.4	129.1	287	143.6	32.95	137.8
	Max Conc (ng/mL)	17	5.45	9.92	19.5	10.57	31.12	10.13
	Time of CMAX (min)	17	30	60	90	68.88	25.56	66.53

Min and max values have been rounded to 3 significant digits. STD, CV, mean, median and geometric mean have been rounded to 4 significant digits

SM17_03 PK parameter data, SAS program: pp_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-29T11:55:04

11.3.5.1 Comparison of test and reference products – pharmacokinetic parameters (non-baseline adjusted data, N=17)

Statistically significant differences between each of the 4 test products and the reference product were shown for AUC_{0-t}, AUC_{60min} and C_{max}, see [Table 14.3-50](#) to [Table 14.3-53](#), [Table 14.3-60](#) to [Table 14.3-63](#) and [Table 14.3-70](#) to [Table 14.3-73](#) (Section 14.3.2.6), respectively.

Mean AUC_{0-t}, AUC_{60min} and C_{max} from the test products containing 3 mg nicotine were significantly lower compared to those of the reference product whereas mean AUC_{0-t}, AUC_{60min} and C_{max} from the test products containing 6 mg were significantly higher compared to the reference product.

There were no statistically significant differences between any of the 4 test products and the reference product in terms of terminal half-life or T_{max}, see [Table 14.3-80](#) to [Table 14.3-83](#) and [Table 14.3-90](#) to [Table 14.3-93](#) (Section 14.3.2), respectively.

11.3.5.2 Pairwise comparison between the test products – pharmacokinetic parameters (non-baseline adjusted data, N=17)

For AUC_{0-t}, AUC_{60min} and C_{max} there were statistically significant differences between:

- ZYN® Smooth 3 mg and 6 mg
- ZYN® Smooth 3 mg and 6 mg (alternative manufacturing process)
- ZYN® Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process)
- ZYN® Smooth 3 mg (alternative manufacturing process) and 6 mg

For T_{max} , there were statistically significant differences between:

- ZYN® Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process)
- ZYN® Smooth 6 mg and 6 mg (alternative manufacturing process)

No other statistically significant differences were observed in the pairwise comparisons between the test products.

Details are provided in [Table 14.3-54](#) to [Table 14.3-59](#), [Table 14.3-64](#) to [Table 14.3-69](#), [Table 14.3-74](#) to [Table 14.3-79](#), [Table 14.3-84](#) to [Table 14.3-89](#) and [Table 14.3-94](#) to [Table 14.3-99](#) (Section 14.3.2).

11.3.5.3 Pairwise comparisons – pharmacokinetic parameters (non-baseline adjusted and baseline adjusted data, N=12)

Additional comparisons are presented in [Table 14.3-101](#) to [Table 14.3-150](#) (Section 14.3.2.7; non-baseline adjusted data, N=12) and [Table 14.3-152](#) to [Table 14.3-201](#) (Section 14.3.2.8; baseline adjusted data, N=12).

11.3.6 Vital signs

11.3.6.1 Comparison between test and reference products – pulse rate

There were no statistically significant differences in change in pulse rate between any of the test products and the reference product at any of the time points, see [Table 14.3-202](#) to [Table 14.3-205](#) (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 beats/min for the reference product compared to 5, 4, 11 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 median change from baseline at 60 min was 8 beats/min for the reference product compared to 8, 5, 10 and 10 beats/min for ZYN® 3 mg, ZYN® 3 mg (alternative manufacturing process), ZYN® 6 mg and ZYN® 6 mg (alternative manufacturing process), respectively.

Descriptive data are summarized in [Table 14.3-212](#) (Section 14.3.2).

11.3.6.2 Pairwise comparison between the test products – pulse rate

There were no statistically significant differences in change in pulse rate between the test products at the majority of time points, see [Table 14.3-206](#) to [Table 14.3-211](#) (Section 14.3.2).

11.3.7 Visual Analogue Scale

11.3.7.1 Comparison between test and reference products – VAS

There were statistically significant differences in change in head buzz (measured by VAS) between the test products and the reference product at a majority of time points, see [Table 14.3-213](#) to [Table 14.3-216](#) (Section 14.3.2).

There was an increase in head buzz in all treatment groups compared to baseline. The increase was larger for the reference product than for either of the test products (3 mg and 6 mg) at all time points. The median change from baseline at 15 min was 24 for the reference product compared to 4, 6, 8 and 7 for ZYN® 3 mg, ZYN® 3 mg (alternative manufacturing process),

ZYN® 6 mg and ZYN® 6 mg (alternative manufacturing process), respectively. The median change from baseline at 60 min was 10 for the reference product compared to 2, 4, 4 and 0 for ZYN® 3 mg, ZYN® 3 mg (alternative manufacturing process), ZYN® 6 mg and ZYN® 6 mg (alternative manufacturing process), respectively.

Descriptive data are summarized in [Table 14.3-223](#) (Section 14.3.2).

11.3.7.2 Pairwise comparison between the test products – VAS

There were no statistically significant differences in change in head buzz (measured by VAS) between the test products at the majority of time points, see [Table 14.3-217](#) to [Table 14.3-222](#) (Section 14.3.2).

11.3.8 Adverse events

Refer to Section 12.

11.4 Statistical/analytical issues

Not applicable.

11.5 Summary of efficacy results

There were statistically significant differences in mean AUC_{inf} between each of the 4 test products and the reference product Swedish portion snus PSWL 1.0 g (8 mg). The AUC_{inf} of the test products containing 3 mg nicotine was significantly lower compared to that of the reference product and the AUC_{inf} of the test products containing 6 mg was significantly higher. There were no statistically significant differences in AUC_{inf} between the ZYN® and ZYN® (alternative manufacturing process) products.

The corresponding result was observed for the extracted amount of nicotine. The extracted amount of nicotine from the test products ZYN® 3 mg and ZYN® 3 mg (alternative manufacturing process) was significantly lower compared to the reference product. The extracted amount from ZYN® 6 mg and ZYN® 6 mg (alternative manufacturing process) was significantly higher compared to the reference product. There was a statistically significant difference in the extracted amount of nicotine between the ZYN® 6 mg and ZYN® 6 mg (alternative manufacturing process) but not between the ZYN® 3 mg and ZYN® 3 mg (alternative manufacturing process).

There were statistically significant differences in rate of extraction between each of the 4 test products and reference product. The rate of extraction for the test products was significantly higher compared to the reference product. There was a statistically significant difference in rate of extraction between the ZYN® 3 mg and ZYN® 3 mg (alternative manufacturing process).

There were statistically significant differences in nicotine plasma concentrations between the 4 test products and the reference products at a majority of time points. The plasma concentrations from the test products containing 3 mg nicotine were significantly lower compared to those of the reference product and the plasma concentrations from the test products containing 6 mg were significantly higher compared to the reference product. There were no statistically significant differences in nicotine plasma concentration between the ZYN® and ZYN® (alternative manufacturing process) products.

For the PK parameters, there were statistically significant differences in AUC_{0-t} , AUC_{60min} and C_{max} between each of the test products and the reference product whereas no statistically significant differences were seen in terms of terminal half life and T_{max} .

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. 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. There were no statistically significant differences in change in pulse rate between the test products at the majority of time points

There were statistically significant differences in head buzz between each of the test products and the reference product at a majority of time points. The change in head buzz was larger in the reference group compared to each of the test products (3 mg and 6 mg) at all time points. There were no statistically significant differences in change in head buzz (measured by VAS) between the test products at the majority of time points.

12 ADVERSE EVENTS

12.1 Brief summary of adverse events

A total of 16 AEs was reported by 8 subjects during the study. There were no SAEs or withdrawals due to AEs.

All AEs were of mild to moderate intensity and most were assessed as unrelated to treatment with IP. Two (2) of the AEs were judged to have a possible or probable relationship to treatment, for details refer to Section 12.3.

A summary of treatment-emergent AEs (TEAEs) 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.

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.

Three (3) baseline events were collected after the subject had signed the ICF and before the first administration of IP, see Table 14.4-3 to Table 14.4-8 and Appendix 16.2.7.

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)	5
ZYN® Smooth 3 mg	1
ZYN® Smooth 3 mg (alt. manu. proc.)	8
ZYN® Smooth 6 mg	1
ZYN® Smooth 6 mg (alt. manu. proc.)	1
Total	16

SM17_03 AE tabulations, SAS program: ae_tabulations_ext.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-12-06T14:57:46

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

Treatment	No	
	AE	AE
Swedish portion snus PSWL 1.0 g (8 mg)	4	13
ZYN® Smooth 3 mg	1	16
ZYN® Smooth 3 mg (alt. manu. proc.)	7	10
ZYN® Smooth 6 mg	1	16
ZYN® Smooth 6 mg (alt. manu. proc.)	1	17

SM17_03 AE tabulations, SAS program: ae_tabulations_ext.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-12-06T14:57:46

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

Treatment	Number of subjects with at least one related AE	Number of subjects with no related AE
Swedish portion snus PSWL 1.0 g (8 mg)	1	16
ZYN® Smooth 3 mg	0	17
ZYN® Smooth 3 mg (alt. manu. proc.)	1	16
ZYN® Smooth 6 mg	0	17
ZYN® Smooth 6 mg (alt. manu. proc.)	0	18

SM17_03 AE tabulations, SAS program: ae_tabulations_ext.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-12-06T14:57:46

12.2 Display of adverse events

Adverse events were most commonly reported within the Infections and infestations SOC; 2 subjects reported nasopharyngitis following treatment with the reference product Swedish portion snus PSWL and 5 subjects reported nasopharyngitis (n=3), tonsillitis (n=1) and urinary tract infection (n=1) following treatment with ZYN® Smooth 3 mg (alternative manufacturing process).

Dry mouth (SOC: gastrointestinal disorders) was reported by 1 subject following treatment with the reference product and ZYN® Smooth 3 mg (alternative manufacturing process), respectively. Dysmenorrhoea (SOC: reproductive system and breast disorders) was reported by 2 subjects following treatment with the reference product and ZYN® Smooth 6 mg (alternative manufacturing process), respectively.

All other AEs were single events reported by single subjects.

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) (N=17)		ZYN® Smooth 3 mg (N=17)		ZYN® Smooth 3 mg (alt. manu. proc.) (N=17)		ZYN® Smooth 6 mg (N=17)		ZYN® Smooth 6 mg (alt. manu. proc.) (N=18)	
	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	5.9%			1	5.9%				
Infections and infestations	2	11.8%			5	29.4%				
Musculoskeletal and connective tissue disorders			1	5.9%	1	5.9%				
Nervous system disorders							1	5.9%		
Renal and urinary disorders	1	5.9%								
Reproductive system and breast disorders	1	5.9%							1	5.6%
Respiratory, thoracic and mediastinal disorders					1	5.9%				

SM17_03 AE tabulations, SAS program: ae_tabulations_ext.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-12-06T14:57:46

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

Body System or Organ Class	Dictionary-Derived Term	Treatment									
		Swedish portion snus PSWL 1.0 g (8 mg) (N=17)		ZYN® Smooth 3 mg (N=17)		ZYN® Smooth 3 mg (alt. manu. proc.) (N=17)		ZYN® Smooth 6 mg (N=17)		ZYN® Smooth 6 mg (alt. manu. proc.) (N=18)	
		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	Dry mouth	1	5.9%			1	5.9%				
Infections and infestations	Nasopharyngitis	2	11.8%			3	17.6%				
	Tonsillitis					1	5.9%				
	Urinary tract infection					1	5.9%				
Musculoskeletal and connective tissue disorders	Back pain			1	5.9%						
	Neck pain					1	5.9%				
Nervous system disorders	Dizziness							1	5.9%		
Renal and urinary disorders	Pollakiuria	1	5.9%								
Reproductive system and breast disorders	Dysmenorrhoea	1	5.9%							1	5.6%
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain					1	5.9%				

SM17_03 AE tabulations, SAS program: ae_tabulations_ext.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-12-06T14:57:46

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

Body System or Organ Class	Dictionary-Derived Term	Causality	Treatment									
			Swedish portion snus PSWL 1.0 g (8 mg) (N=17)		ZYN® Smooth 3 mg (N=17)		ZYN® Smooth 3 mg (alt. manu. proc.) (N=17)		ZYN® Smooth 6 mg (N=17)		ZYN® Smooth 6 mg (alt. manu. proc.) (N=18)	
			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	Dry mouth	POSSIBLE	1	5.9%								
		PROBABLE					1	5.9%				
Infections and infestations	Nasopharyngitis	NOT RELATED	2	11.8%			3	17.6%				
	Tonsillitis	NOT RELATED					1	5.9%				
	Urinary tract infection	NOT RELATED					1	5.9%				
Musculoskeletal and connective tissue disorders	Back pain	NOT RELATED			1	5.9%						
	Neck pain	NOT RELATED					1	5.9%				
Nervous system disorders	Dizziness	NOT RELATED							1	5.9%		
Renal and urinary disorders	Pollakiuria	NOT RELATED	1	5.9%								
Reproductive system and breast disorders	Dysmenorrhoea	NOT RELATED	1	5.9%							1	5.6%
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	NOT RELATED					1	5.9%				

SM17_03 AE tabulations, SAS program: ae_tabulations_ext.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-12-06T14:57:46

12.3 Analysis of adverse events

One subject (Subject 111) reported dry mouth twice assessed as probably and possibly related to treatment with IP, respectively. The first event was associated with treatment with the reference product whereas the second event was associated with treatment with ZYN[®] Smooth 3 mg (alternative manufacturing process). All other AEs were assessed as “not related” by the investigator. All AEs were resolved at 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 16 AEs was reported by 8 subjects during the study and 2 (dry mouth) were judged to have a possible or probable relationship to treatment. There were no SAEs or discontinuations due to AEs during the study.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

This open, randomized, 5-way cross-over study compared the PK and subjective effects of nicotine following a single dose of a non-tobacco-based nicotine pouch (ZYN[®]) containing either 3 mg or 6 mg nicotine and a single dose of conventional, tobacco-based Swedish snus (PSWL) containing 8 mg nicotine in 18 daily snus users. Two (2) 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 and the resulting uptake to the systemic blood circulation, measured as AUC_{inf}, based on plasma concentrations of nicotine, versus a conventional snus pouch. The extraction and plasma data were supplemented with assessments of subjective effects of “product strength” and pulse rate measurements, both of which constitute proxies for systemic nicotine uptake.

A single dose of Swedish snus PSWL 1.0 g (8 mg nicotine/g) resulted in significantly higher mean nicotine AUC_{inf} compared to both ZYN[®] 3 mg and ZYN[®] 3 mg (alternative manufacturing process). In contrast, single doses of ZYN[®] 6 mg and ZYN[®] 6 mg (alternative

manufacturing process), respectively, both resulted in significantly higher mean nicotine AUC_{inf} , compared to a single dose of Swedish portion snus PSWL 1.0 g (8 mg nicotine/g), which was an unexpected finding. Rather, it was expected that the extraction and absorption of nicotine would correlate with the amount of nicotine in each product and hence that a single dose of PSWL 1.0 g (8 mg nicotine/g) would result in a higher nicotine AUC_{inf} than a single dose of either ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process).

There were no statistically significant differences in AUC_{inf} between ZYN[®] 3 mg and ZYN[®] 3 mg (alternative manufacturing process), nor ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process).

In line with the results for AUC_{inf} , the extracted amount of nicotine was lower for the ZYN[®] 3 mg pouches and higher for the ZYN[®] 6 mg pouches compared to that from the PSWL 8 mg pouch. Unexpectedly, there was also a statistically significant difference in extracted amount of nicotine between ZYN[®] 6 mg and ZYN[®] 6 mg (alternative manufacturing process). However, this difference is completely explained by the unintended somewhat lower nicotine content in ZYN[®] 6 mg (alternative manufacturing process), as shown by the equal values for the rate of extraction for the 2 products. In addition, due to the small difference in observed median values between the 2 test products (0.7 mg), the effect of multiple testing and the absence of any control of keeping the total significance level on 5%, this finding is likely a pure chance finding. Had a p-value adjustment method, due to multiple testing, been applied, the result would have been concluded as non-significant. Therefore, all results for extracted amount of nicotine is judged to be in line with the results for AUC_{inf} .

In general, corresponding results to those obtained for AUC_{inf} and extracted amount of nicotine, were obtained also for nicotine plasma concentrations, AUC_{0-t} , AUC_{60min} and C_{max} . There were however, no statistically significant differences between the test products and the reference product in terms of terminal half-life and T_{max} .

Despite statistically significant differences between each of the test products and the reference product for all primary and secondary endpoints related to PK, there were no statistically significant differences between the groups in terms of change in pulse rate, i.e. the higher AUC_{inf} and extracted amount of nicotine observed in the ZYN[®] 6 mg groups did not result in a significantly larger change in pulse rate compared to the change in the PSWL group.

For head buzz (measured by a VAS), there were, in general, statistically significant differences between each of the test products and the reference product from approximately 15 min until 60 min after dose. Interestingly, the mean VAS score was always higher following intake of PSWL 1.0 g (8 mg nicotine/g) than after intake of any of the ZYN products (3 mg and 6 mg) despite a higher AUC_{inf} and extracted amount of nicotine in the ZYN[®] 6 mg groups, i.e. there was no obvious correlation between high nicotine levels and head buzz. Potentially, another component of conventional snus, e.g. tobacco, contributes to the feeling of head buzz. It should be noted that this was an open study and the subjects knew when they were administered conventional snus, which may have resulted in bias during the VAS assessment.

13.2 OVERALL CONCLUSIONS

Despite a lower nicotine content, the non-tobacco-based ZYN[®] 6 mg products gave rise to significantly larger nicotine extraction and subsequent uptake of nicotine in the systemic blood circulation than did the conventional, tobacco-based snus (PSWL) 8 mg product. The larger nicotine exposure was not associated with a statistically significantly larger increase in

pulse rate in the ZYN® 6 mg group compared to the PSWL group. Interestingly, the increase in head buzz was statistically significantly smaller in the ZYN® 6 mg group compared to the PSWL group.

Conventional, tobacco-based snus (PSWL) 8 mg gave rise to significantly larger nicotine extraction and subsequent uptake in the systemic blood circulation than did the non-tobacco-based ZYN® 3 mg products. The effect was not associated with a larger increase in pulse rate in the PSWL group compared to the ZYN® 3 mg group but was associated with a larger increase in head buzz in the PSWL group.

Both the test and the reference products 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	4	4	4
WITHDRAWAL OF CONSENT			1	

SM17_03 disposition data, SAS program: subject_disposition.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:56:03

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	4	5	4
Screening	5	4	5	4
Visit 2	5	4	5	4
Visit 3	5	4	4	4
Visit 4	5	4	4	4
Visit 5	5	4	4	4
Visit 6	5	4	4	4
Visit 7 Follow-up	5	4	4	4
Visit 8 End of Study	5	4	5	4

SM17_03 disposition data, SAS program: subject_disposition.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:56:03

Table 14.1-3 Nicotine abstinence

Product	Abstinence result	
	No	Yes
Screening	2	18
ZYN® Smooth 3 mg		17
ZYN® Smooth 6 mg		17
ZYN® Smooth 3 mg (alt. manu. proc.)		17
ZYN® Smooth 6 mg (alt. manu. proc.)		18
Swedish portion snus PSWL 1.0 g (8 mg)		17

SM17_03 disposition data, SAS program: subject_disposition.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:56:03

14.2 Demographic data and other baseline characteristics

Reported in-text, see Section 10.4.

14.3 Primary and secondary endpoints

14.3.1 Primary endpoint

14.3.1.1 Difference in AUC_{inf} (non-baseline adjusted, N=17)

Table 14.3-1 Difference in AUC_{inf} (min*ng/mL): ZYN® Smooth 3 mg vs. ZYN® Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.5498
Mean (Std)	1906.77 (911.35)	1979.21 (1168.37)	-72.44 (488.82)	Signed Rank	0.9265
Median (min;max)	1687.57 (835.27;4643)	1610.05 (449.58;5401.61)	91.81 (-1206.65;726.65)		
Q1, Q3 (IQR)	1374.18 2297.52 (923.34)	1321.68 2260.9 (939.22)	-321.79 176.28 (498.07)		

SM17_03 Analysis of secondary endpoint - AUC_{inf} , SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 14.3-2 Difference in AUC_{inf} (min*ng/mL): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1906.77 (911.35)	3581.26 (1541.27)	-1674.49 (994.58)	Signed Rank	<.0001
Median (min;max)	1687.57 (835.27;4643)	3329.25 (1281.45;7556.81)	-1545.42 (-3438.21;28.64)		
Q1, Q3 (IQR)	1374.18 2297.52 (923.34)	2753.12 4476.15 (1723.03)	-2205.42 -1225.63 (979.79)		

SM17_03 Analysis of secondary endpoint - AUC_{inf} , SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 14.3-3 Difference in AUC_{inf} (min*ng/mL): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1906.77 (911.35)	3453.7 (1792.41)	-1546.93 (1030.52)	Signed Rank	<.0001
Median (min;max)	1687.57 (835.27;4643)	3202.21 (1334.97;9385.28)	-1344.3 (-4742.27;-315.06)		
Q1, Q3 (IQR)	1374.18 2297.52 (923.34)	2535.08 3964.3 (1429.22)	-1967.07 -1003.47 (963.6)		

SM17_03 Analysis of secondary endpoint - AUC_{inf} , SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 14.3-4 Difference in AUC_{inf} (min*ng/mL): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1979.21 (1168.37)	3581.26 (1541.27)	-1602.06 (768.62)	Signed Rank	<.0001
Median (min;max)	1610.05 (449.58;5401.61)	3329.25 (1281.45;7556.81)	-1452.88 (-3321.77;-125.26)		
Q1, Q3 (IQR)	1321.68 2260.9 (939.22)	2753.12 4476.15 (1723.03)	-2094.5 -1068.35 (1026.15)		

SM17_03 Analysis of secondary endpoint - AUC_{inf}, SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 14.3-5 *Difference in AUC_{inf} (min*ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)*

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1979.21 (1168.37)	3453.7 (1792.41)	-1474.49 (841.16)	Signed Rank	<.0001
Median (min;max)	1610.05 (449.58;5401.61)	3202.21 (1334.97;9385.28)	-1204.79 (-3983.67;-468.97)		
Q1, Q3 (IQR)	1321.68 2260.9 (939.22)	2535.08 3964.3 (1429.22)	-1618.22 -1068.67 (549.55)		

SM17_03 Analysis of secondary endpoint - AUC_{inf}, SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

Table 14.3-6 *Difference in AUC_{inf} (min*ng/mL): ZYN[®] Smooth 6 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)*

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.5293
Mean (Std)	3581.26 (1541.27)	3453.7 (1792.41)	127.56 (817.99)	Signed Rank	0.4586
Median (min;max)	3329.25 (1281.45;7556.81)	3202.21 (1334.97;9385.28)	66.84 (-1828.47;1396.78)		
Q1, Q3 (IQR)	2753.12 4476.15 (1723.03)	2535.08 3964.3 (1429.22)	-325.39 532.53 (857.92)		

SM17_03 Analysis of secondary endpoint - AUC_{inf}, SAS program: primary_endpoint.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:13

14.3.1.2 Difference in AUC_{inf} (non-baseline adjusted, N=12)

Table 14.3-7 *Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)*

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1500.85 (485.18)	2135.04 (567.36)	-634.18 (370.94)	Signed Rank	0.0005
Median (min;max)	1415.69 (827.45;2683.86)	2159.15 (1405.88;3397.28)	-664.58 (-1210.71;-1.14)		
Q1, Q3 (IQR)	1190.92 1715.42 (524.5)	1696.69 2383.43 (686.74)	-877.99 -360.38 (517.61)		

SM17_03 Analysis of primary endpoint - AUC_{inf}, SAS program: Difference_in_AUCinf.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-8 *Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg*

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1500.85 (485.18)	2987.22 (1060.66)	-1486.37 (853.54)	Signed Rank	0.0010
Median (min;max)	1415.69 (827.45;2683.86)	3141.78 (1255.57;4928.65)	-1434.34 (-3274.5;35.04)		
Q1, Q3 (IQR)	1190.92 1715.42 (524.5)	2397.5 3410.99 (1013.49)	-1990.68 -1109.08 (881.6)		

SM17_03 Analysis of primary endpoint - AUC_{inf}, SAS program: Difference_in_AUCinf.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-9 *Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)*

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0813
Mean (Std)	1500.85 (485.18)	1403.17 (454.13)	97.69 (176.37)	Signed Rank	0.0522
Median (min;max)	1415.69 (827.45;2683.86)	1365.67 (509.64;2327.65)	122.33 (-305.79;356.2)		
Q1, Q3 (IQR)	1190.92 1715.42 (524.5)	1169.78 1606.12 (436.34)	14.35 182.18 (167.83)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-10 *Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)*

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1500.85 (485.18)	2747.45 (924.09)	-1246.59 (639.6)	Signed Rank	0.0005
Median (min;max)	1415.69 (827.45;2683.86)	2652.91 (1309.81;4590.8)	-1126.38 (-2251.94;-310.92)		
Q1, Q3 (IQR)	1190.92 1715.42 (524.5)	2096.59 3214.02 (1117.43)	-1901.34 -776.2 (1125.14)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-11 *Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)*

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0044
Mean (Std)	2987.22 (1060.66)	2135.04 (567.36)	852.19 (827.46)	Signed Rank	0.0024
Median (min;max)	3141.78 (1255.57;4928.65)	2159.15 (1405.88;3397.28)	848.68 (-438.6;2586.98)		
Q1, Q3 (IQR)	2397.5 3410.99 (1013.49)	1696.69 2383.43 (686.74)	536.8 1178.52 (641.72)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-12 *Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)*

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	2987.22 (1060.66)	1403.17 (454.13)	1584.05 (799.36)	Signed Rank	0.0005
Median (min;max)	3141.78 (1255.57;4928.65)	1365.67 (509.64;2327.65)	1569.81 (124.35;3304.74)		
Q1, Q3 (IQR)	2397.5 3410.99 (1013.49)	1169.78 1606.12 (436.34)	1133.15 2003 (869.85)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-13 *Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)*

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.2171
Mean (Std)	2987.22 (1060.66)	2747.45 (924.09)	239.78 (634.34)	Signed Rank	0.2661
Median (min;max)	3141.78 (1255.57;4928.65)	2652.91 (1309.81;4590.8)	141.36 (-896.38;1266.54)		
Q1, Q3 (IQR)	2397.5 3410.99 (1013.49)	2096.59 3214.02 (1117.43)	157.21 774.18 (931.39)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-14 Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1403.17 (454.13)	2135.04 (567.36)	-731.87 (384.5)	Signed Rank	0.0005
Median (min;max)	1365.67 (509.64;2327.65)	2159.15 (1405.88;3397.28)	-641.84 (-1369.56;-121.95)		
Q1, Q3 (IQR)	1169.78 1606.12 (436.34)	1696.69 2383.43 (686.74)	-1099.3 -421.54 (677.76)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-15 Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1403.17 (454.13)	2747.45 (924.09)	-1344.28 (603.83)	Signed Rank	0.0005
Median (min;max)	1365.67 (509.64;2327.65)	2652.91 (1309.81;4590.8)	-1160.46 (-2282.17;-470.32)		
Q1, Q3 (IQR)	1169.78 1606.12 (436.34)	2096.59 3214.02 (1117.43)	-1846.83 -917.52 (929.31)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

Table 14.3-16 Difference in AUC_{inf} (min*ng/mL): ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0150
Mean (Std)	2747.45 (924.09)	2135.04 (567.36)	612.41 (736.99)	Signed Rank	0.0210
Median (min;max)	2652.91 (1309.81;4590.8)	2159.15 (1405.88;3397.28)	712.96 (-633.07;1660.41)		
Q1, Q3 (IQR)	2096.59 3214.02 (1117.43)	1696.69 2383.43 (686.74)	-22.77 1120.75 (1143.52)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} .sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:26:11

14.3.1.3 Difference in AUC_{inf} (baseline adjusted, N=12)

Table 14.3-17 Difference in AUC_{inf} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1322.58 (474.65)	2006.78 (526.09)	-684.2 (346.82)	Signed Rank	0.0005
Median (min;max)	1214.65 (694.85;2506.51)	2066.1 (1329.1;3170.54)	-658.04 (-1257.66;-109.21)		
Q1, Q3 (IQR)	1027.59 1531.9 (504.31)	1613.65 2230.03 (616.38)	-979.89 -442.16 (537.73)		

SM17_03 Analysis of primary endpoint - AUC_{inf} , SAS program: Difference_in_ AUC_{inf} _with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21

Table 14.3-18 Difference in AUC_{inf} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1322.58 (474.65)	2847.34 (1021.25)	-1524.76 (788.52)	Signed Rank	0.0005
Median (min;max)	1214.65 (694.85;2506.51)	3007.95 (1240.65;4630.97)	-1452.16 (-3093.33;-113.06)		
Q1, Q3 (IQR)	1027.59 1531.9 (504.31)	2311.75 3249.51 (937.76)	-2000.34 -1198.84 (801.5)		

SM17_03 Analysis of primary endpoint - AUC_{inf}, SAS program: Difference_in_AUCinf_with_bsl.sas.
Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21

Table 14.3-19 Difference in AUC_{inf} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.3118
Mean (Std)	1322.58 (474.65)	1265.83 (399.18)	56.75 (185.43)	Signed Rank	0.2334
Median (min;max)	1214.65 (694.85;2506.51)	1233.14 (509.64;2134.3)	58.8 (-318.81;372.21)		
Q1, Q3 (IQR)	1027.59 1531.9 (504.31)	1071.31 1511.05 (439.74)	-42.87 178.3 (221.17)		

SM17_03 Analysis of primary endpoint - AUC_{inf}, SAS program: Difference_in_AUCinf_with_bsl.sas.
Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21

Table 14.3-20 Difference in AUC_{inf} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1322.58 (474.65)	2569.41 (922.79)	-1246.83 (629.79)	Signed Rank	0.0005
Median (min;max)	1214.65 (694.85;2506.51)	2546.5 (1200.63;4437.41)	-1168.62 (-2082.38;-228.39)		
Q1, Q3 (IQR)	1027.59 1531.9 (504.31)	1983.29 3033.2 (1049.91)	-1903.19 -780 (1123.19)		

SM17_03 Analysis of primary endpoint - AUC_{inf}, SAS program: Difference_in_AUCinf_with_bsl.sas.
Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21

Table 14.3-21 Difference in AUC_{inf} (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0035
Mean (Std)	2847.34 (1021.25)	2006.78 (526.09)	840.56 (788.36)	Signed Rank	0.0024
Median (min;max)	3007.95 (1240.65;4630.97)	2066.1 (1329.1;3170.54)	855.76 (-383.03;2441.29)		
Q1, Q3 (IQR)	2311.75 3249.51 (937.76)	1613.65 2230.03 (616.38)	503.98 1086.08 (582.1)		

SM17_03 Analysis of primary endpoint - AUC_{inf}, SAS program: Difference_in_AUCinf_with_bsl.sas.
Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21

Table 14.3-22 Difference in AUC_{inf} (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	2847.34 (1021.25)	1265.83 (399.18)	1581.51 (761.94)	Signed Rank	0.0005
Median (min;max)	3007.95 (1240.65;4630.97)	1233.14 (509.64;2134.3)	1655.06 (153.67;3111.22)		
Q1, Q3 (IQR)	2311.75 3249.51 (937.76)	1071.31 1511.05 (439.74)	1142.65 2008.87 (866.22)		

SM17_03 Analysis of primary endpoint - AUC_{inf}, SAS program: Difference_in_AUCinf_with_bsl.sas.
Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21

Table 14.3-23 Difference in AUC_{inf} (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1424
Mean (Std)	2847.34 (1021.25)	2569.41 (922.79)	277.93 (609.37)	Signed Rank	0.1294
Median (min;max)	3007.95 (1240.65;4630.97)	2546.5 (1200.63;4437.41)	127.49 (-826.21;1269.19)		

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
Q1, Q3 (IQR)	2311.75 3249.51 (937.76)	1983.29 3033.2 (1049.91)	-66.66 756.13 (822.79)		
SM17_03 Analysis of primary endpoint - AUCinf, SAS program: Difference_in_AUCinf_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21					

Table 14.3-24 *Difference in AUC_{inf}, with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)*

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1265.83 (399.18)	2006.78 (526.09)	-740.95 (353.65)	Signed Rank	0.0005
Median (min;max)	1233.14 (509.64;2134.3)	2066.1 (1329.1;3170.54)	-617.93 (-1250.45;-233.69)		
Q1, Q3 (IQR)	1071.31 1511.05 (439.74)	1613.65 2230.03 (616.38)	-1082.61 -470.95 (611.66)		
SM17_03 Analysis of primary endpoint - AUCinf, SAS program: Difference_in_AUCinf_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21					

Table 14.3-25 *Difference in AUC_{inf}, with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)*

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1265.83 (399.18)	2569.41 (922.79)	-1303.58 (631.76)	Signed Rank	0.0005
Median (min;max)	1233.14 (509.64;2134.3)	2546.5 (1200.63;4437.41)	-1195.77 (-2303.11;-269)		
Q1, Q3 (IQR)	1071.31 1511.05 (439.74)	1983.29 3033.2 (1049.91)	-1807.64 -862.93 (944.71)		
SM17_03 Analysis of primary endpoint - AUCinf, SAS program: Difference_in_AUCinf_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21					

Table 14.3-26 *Difference in AUC_{inf}, with baseline adjustment: ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)*

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0232
Mean (Std)	2569.41 (922.79)	2006.78 (526.09)	562.64 (739.79)	Signed Rank	0.0210
Median (min;max)	2546.5 (1200.63;4437.41)	2066.1 (1329.1;3170.54)	639.71 (-580.76;1620.91)		
Q1, Q3 (IQR)	1983.29 3033.2 (1049.91)	1613.65 2230.03 (616.38)	-121.19 1159.67 (1280.86)		
SM17_03 Analysis of primary endpoint - AUCinf, SAS program: Difference_in_AUCinf_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:43:21					

14.3.2 Secondary endpoints

14.3.2.1 Extracted amount of nicotine

Table 14.3-27 *Difference in extracted nicotine (mg): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)*

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0648
Mean (Std)	1.51 (0.6)	1.67 (0.51)	-0.16 (0.34)	Signed Rank	0.0695
Median (min;max)	1.45 (0.6;2.65)	1.58 (0.53;2.61)	-0.12 (-0.95;0.31)		
Q1, Q3 (IQR)	0.99 1.82 (0.83)	1.51 2.1 (0.59)	-0.17 0.04 (0.21)		
SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program: sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13					

Table 14.3-28 Difference in extracted nicotine (mg): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1.51 (0.6)	3.77 (1.17)	-2.26 (0.76)	Signed Rank	<.0001
Median (min;max)	1.45 (0.6;2.65)	3.73 (1.7;5.84)	-2.5 (-3.34;-0.74)		
Q1, Q3 (IQR)	0.99 1.82 (0.83)	3.11 4.88 (1.77)	-2.76 -1.78 (0.98)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-29 Difference in extracted nicotine (mg): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1.51 (0.6)	3.24 (1)	-1.74 (0.62)	Signed Rank	<.0001
Median (min;max)	1.45 (0.6;2.65)	3.53 (1.4;5.09)	-1.89 (-2.7;-0.55)		
Q1, Q3 (IQR)	0.99 1.82 (0.83)	2.64 3.75 (1.11)	-2.13 -1.47 (0.66)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-30 Difference in extracted nicotine (mg): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1.67 (0.51)	3.77 (1.17)	-2.1 (0.73)	Signed Rank	<.0001
Median (min;max)	1.58 (0.53;2.61)	3.73 (1.7;5.84)	-2 (-3.23;-0.59)		
Q1, Q3 (IQR)	1.51 2.1 (0.59)	3.11 4.88 (1.77)	-2.78 -1.66 (1.12)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-31 Difference in extracted nicotine (mg): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1.67 (0.51)	3.24 (1)	-1.57 (0.73)	Signed Rank	<.0001
Median (min;max)	1.58 (0.53;2.61)	3.53 (1.4;5.09)	-1.56 (-2.86;-0.27)		
Q1, Q3 (IQR)	1.51 2.1 (0.59)	2.64 3.75 (1.11)	-2.08 -1.09 (0.99)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program:
sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-32 Difference in extracted nicotine (mg): ZYN® Smooth 6 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0204
Mean (Std)	3.77 (1.17)	3.24 (1)	0.52 (0.84)	Signed Rank	0.0337
Median (min;max)	3.73 (1.7;5.84)	3.53 (1.4;5.09)	0.73 (-1.35;1.73)		
Q1, Q3 (IQR)	3.11 4.88 (1.77)	2.64 3.75 (1.11)	0.19 1.13 (0.94)		

SM17_03 Analysis of secondary endpoint - Extracted nicotine, SAS program: sec_endpoint_extracted.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-33 Difference in rate of extraction (%): ZYN® Smooth 3 mg vs. ZYN® Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0226
Mean (Std)	52.18 (20.98)	59.63 (18.17)	-7.45 (12.18)	Signed Rank	0.0267
Median (min;max)	50.2 (20.99;92.09)	56.72 (18.95;93.08)	-5.26 (-35.73;8.83)		
Q1, Q3 (IQR)	34.24 62.94 (28.7)	54.11 75.21 (21.1)	-7.44 -0.99 (6.45)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

Table 14.3-34 Difference in rate of extraction (%): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0301
Mean (Std)	52.18 (20.98)	59.17 (18.04)	-6.98 (12.1)	Signed Rank	0.0569
Median (min;max)	50.2 (20.99;92.09)	59.41 (26.4;91.5)	-4.96 (-31.35;7.47)		
Q1, Q3 (IQR)	34.24 62.94 (28.7)	49.19 75.98 (26.79)	-11.7 1.64 (13.34)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

Table 14.3-35 Difference in rate of extraction (%): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0333
Mean (Std)	52.18 (20.98)	59.07 (18.2)	-6.89 (12.19)	Signed Rank	0.0638
Median (min;max)	50.2 (20.99;92.09)	63.6 (25.4;92.8)	-3.14 (-32.95;8)		
Q1, Q3 (IQR)	34.24 62.94 (28.7)	48.51 67.42 (18.91)	-17.08 1.62 (18.7)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

Table 14.3-36 Difference in rate of extraction (%): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.8016
Mean (Std)	59.63 (18.17)	59.17 (18.04)	0.47 (7.51)	Signed Rank	0.9632

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
Median (min;max)	56.72 (18.95;93.08)	59.41 (26.4;91.5)	-0.9 (-14.57;13.89)		
Q1, Q3 (IQR)	54.11 75.21 (21.1)	49.19 75.98 (26.79)	-3.52 4.71 (8.23)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

Table 14.3-37 Difference in rate of extraction (%): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.8717
Mean (Std)	59.63 (18.17)	59.07 (18.2)	0.56 (14.12)	Signed Rank	0.4586
Median (min;max)	56.72 (18.95;93.08)	63.6 (25.4;92.8)	2.21 (-29.76;31.69)		
Q1, Q3 (IQR)	54.11 75.21 (21.1)	48.51 67.42 (18.91)	-3.94 6.23 (10.17)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

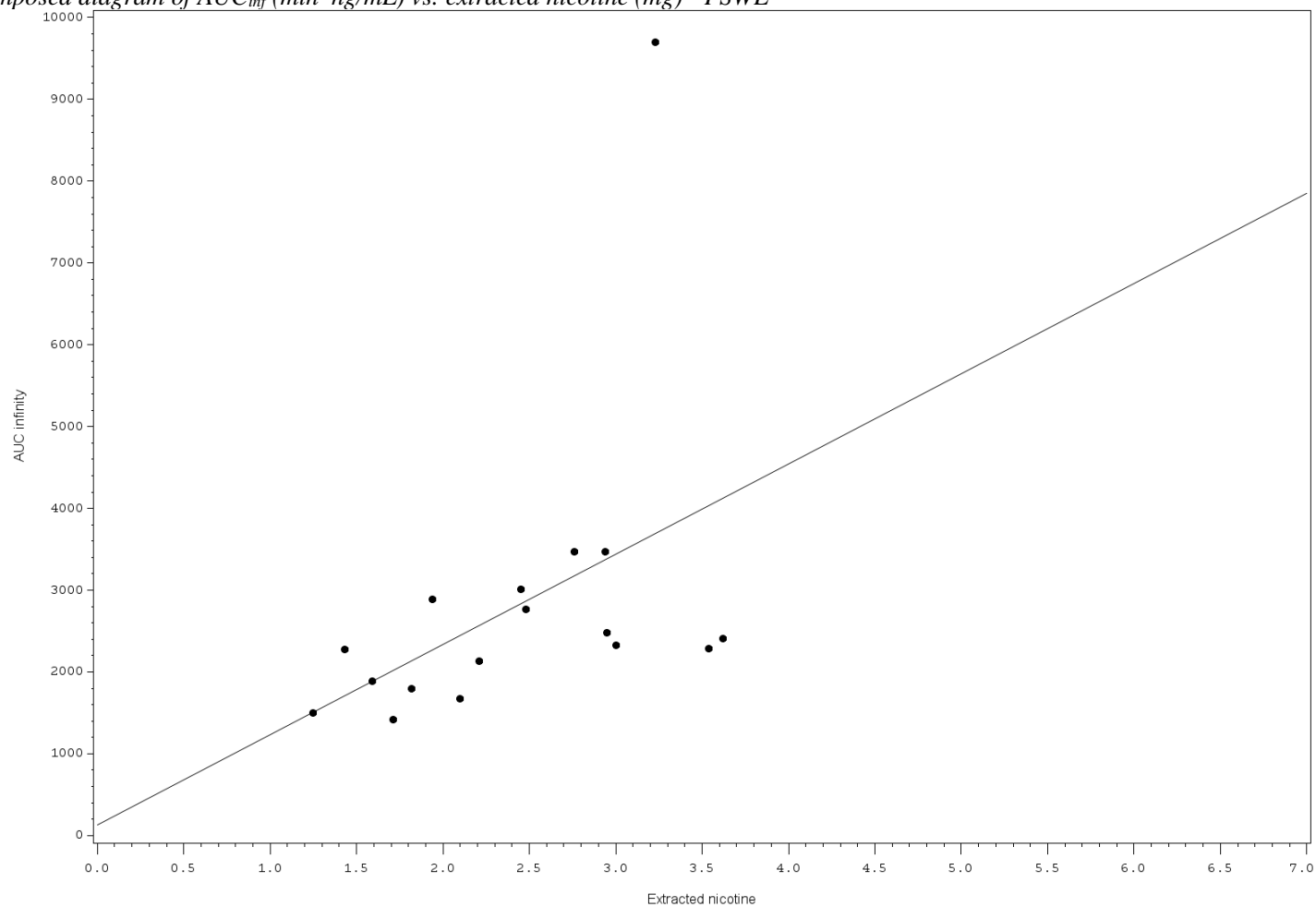
Table 14.3-38 Difference in rate of extraction (%): ZYN® Smooth 6 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.9772
Mean (Std)	59.17 (18.04)	59.07 (18.2)	0.1 (13.71)	Signed Rank	0.6441
Median (min;max)	59.41 (26.4;91.5)	63.6 (25.4;92.8)	3.5 (-30.23;21.26)		
Q1, Q3 (IQR)	49.19 75.98 (26.79)	48.51 67.42 (18.91)	-3.56 8.56 (12.12)		

SM17_03 Analysis of extraction grade, SAS program: Primary_endpoint_extraction_grade.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-06-28T12:27:47

14.3.2.2 Correlations AUC_{inf} and extracted nicotine (non-baseline adjusted data, N=17)

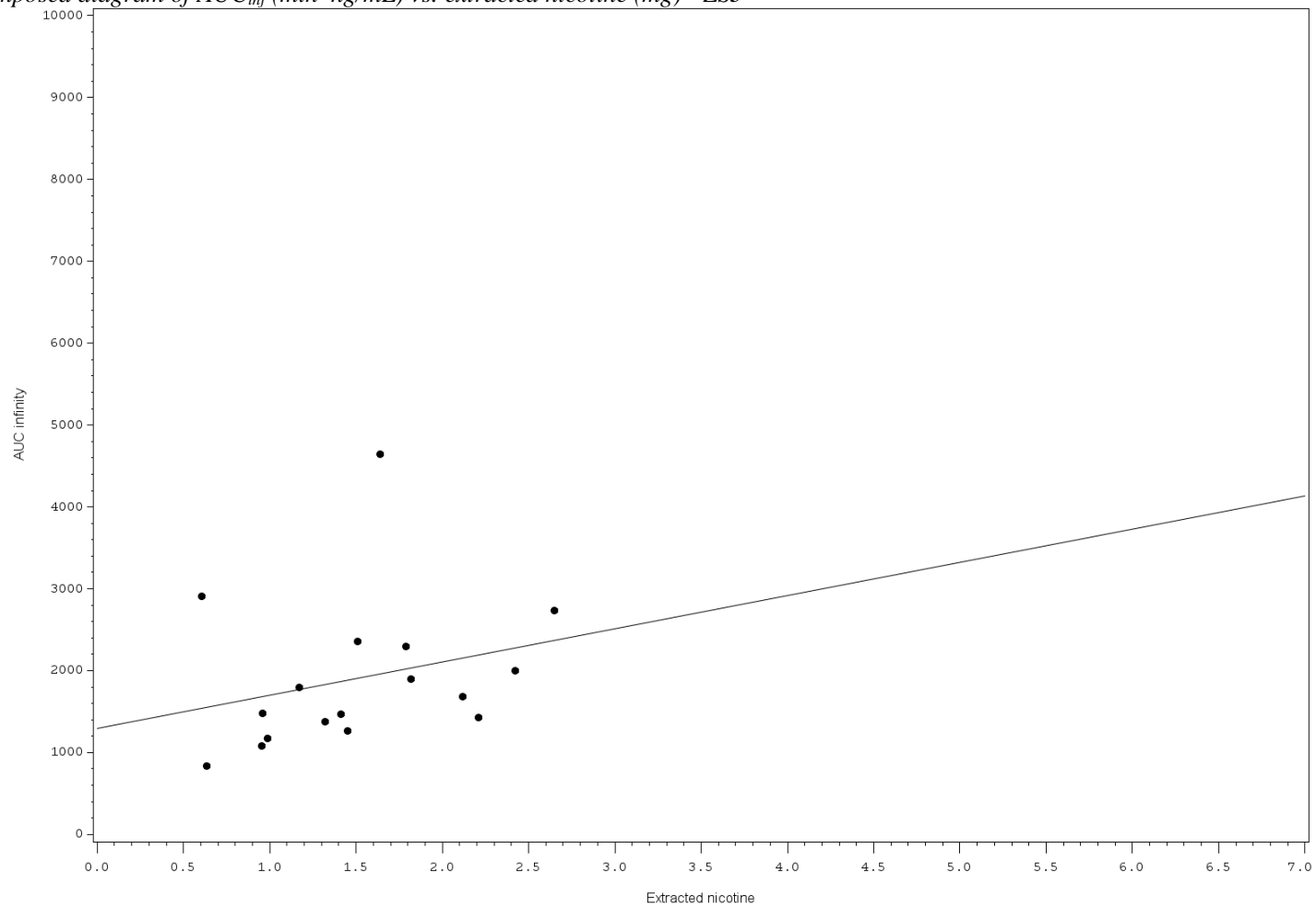
Figure 14.3-1 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine (mg) - PSWL



Regression Equation:
 $AUC = 135.1818 + 1101.544 \cdot EXT_nic$

RSQUARE=0.1845854587

Figure 14.3-2 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine (mg) - ZS3



Regression Equation:
 $AUC = 1294.899 + 405.5279 \cdot EXT_nic$

RSQUARE=0.0720100649

Figure 14.3-3 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine (mg) - ZSA3

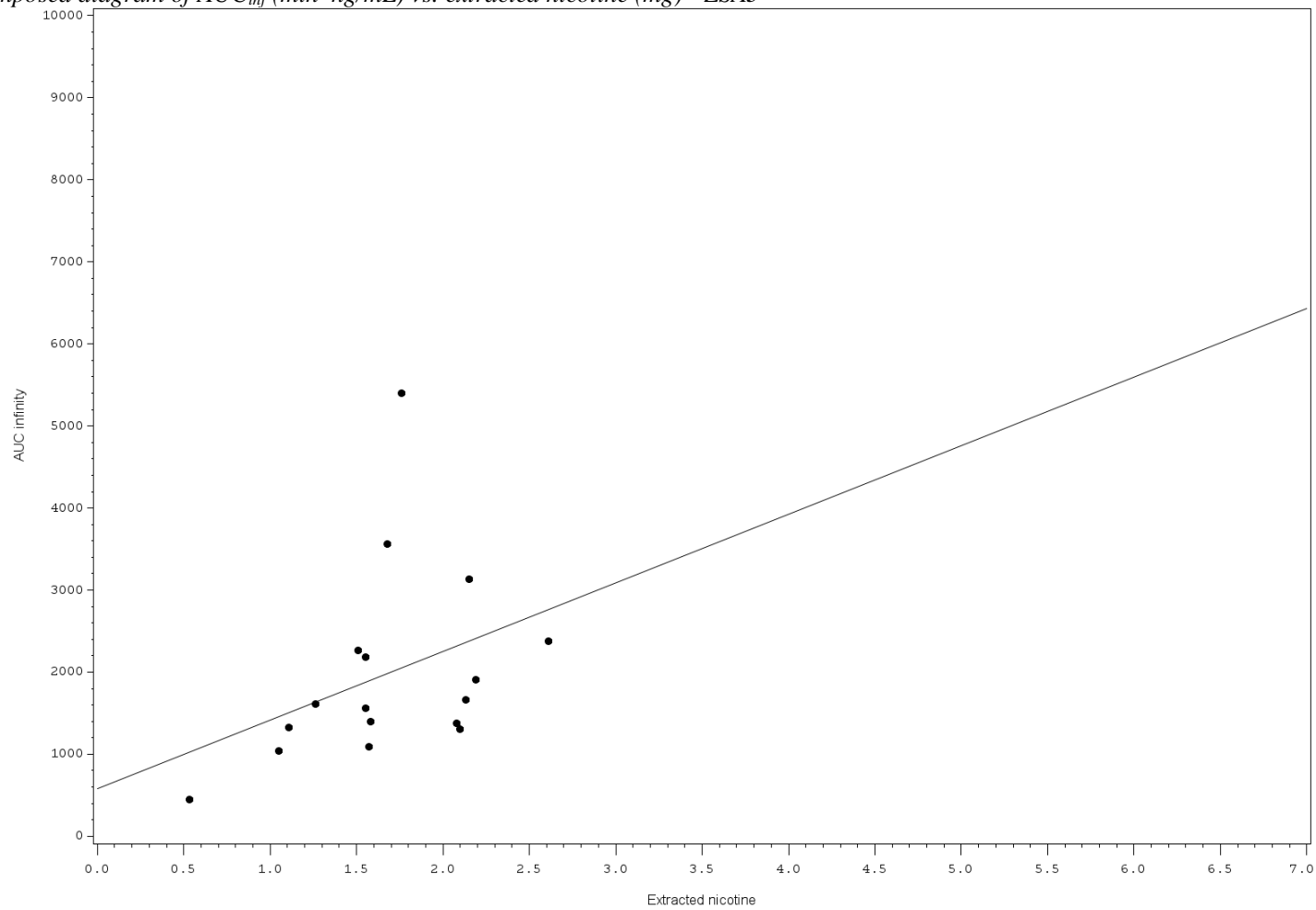
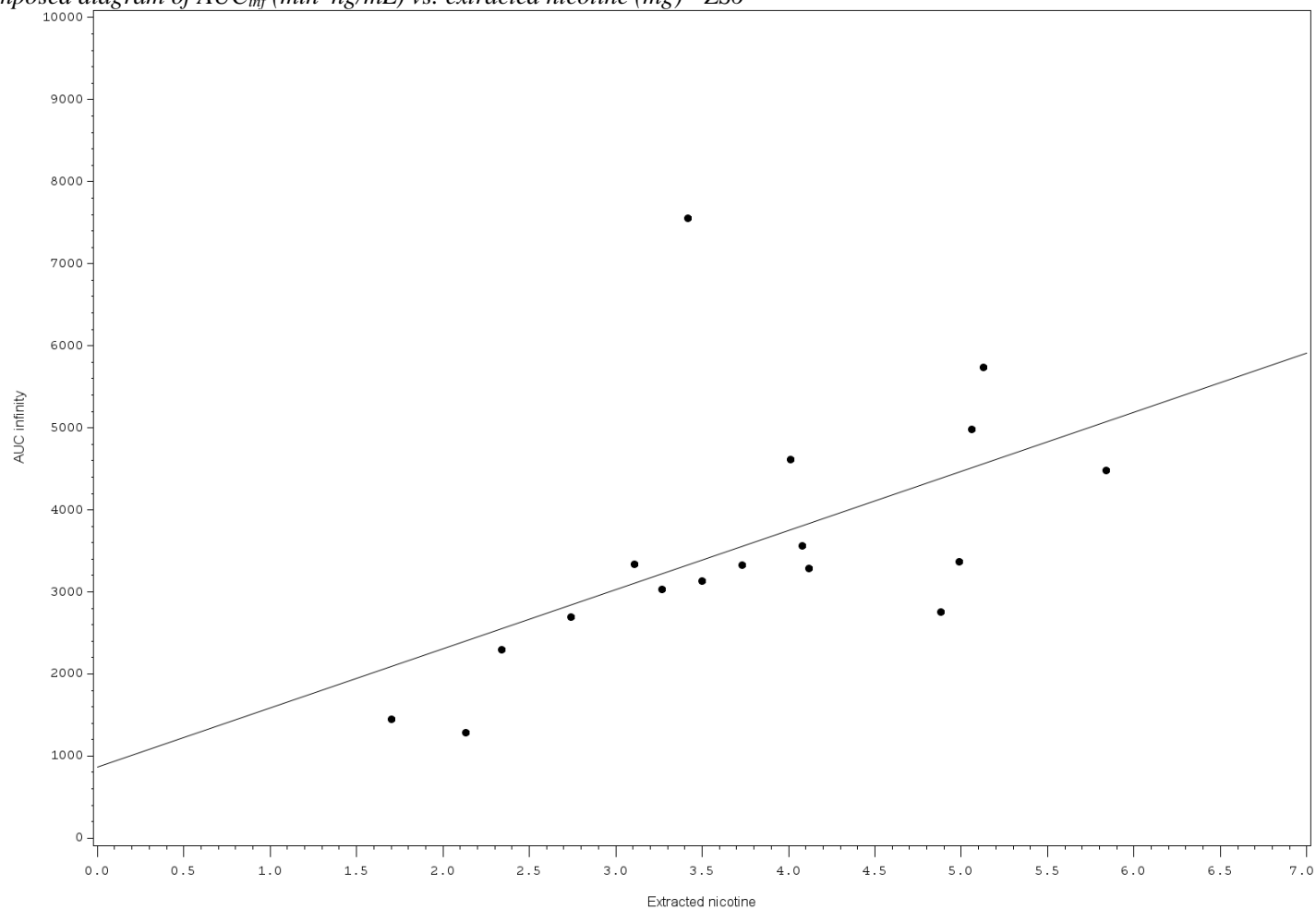


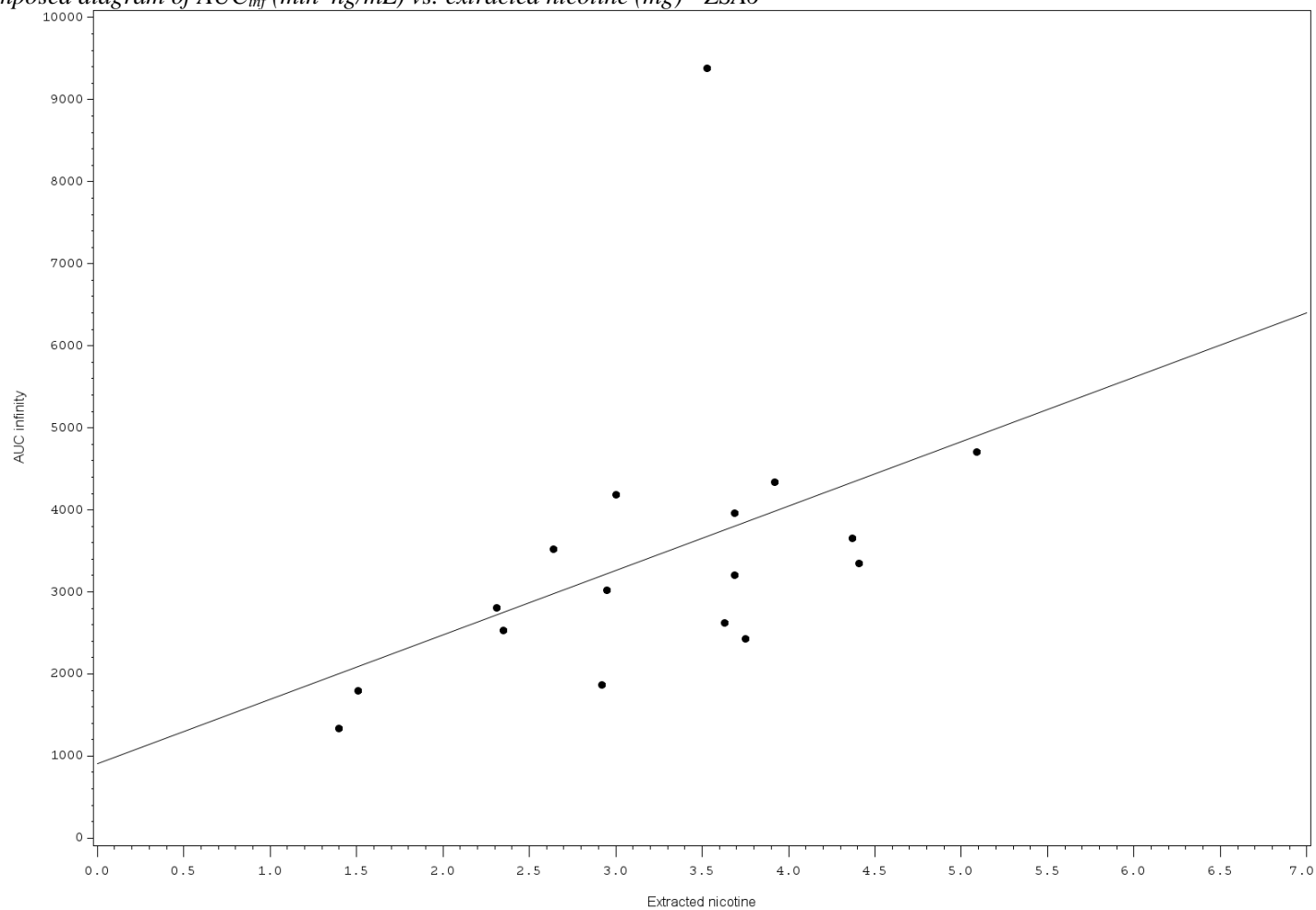
Figure 14.3-4 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine (mg) - ZS6



Regression Equation:
 $AUC = 869.3378 + 719.7927 \cdot EXT_nic$

RSQUARE=0.2965930016

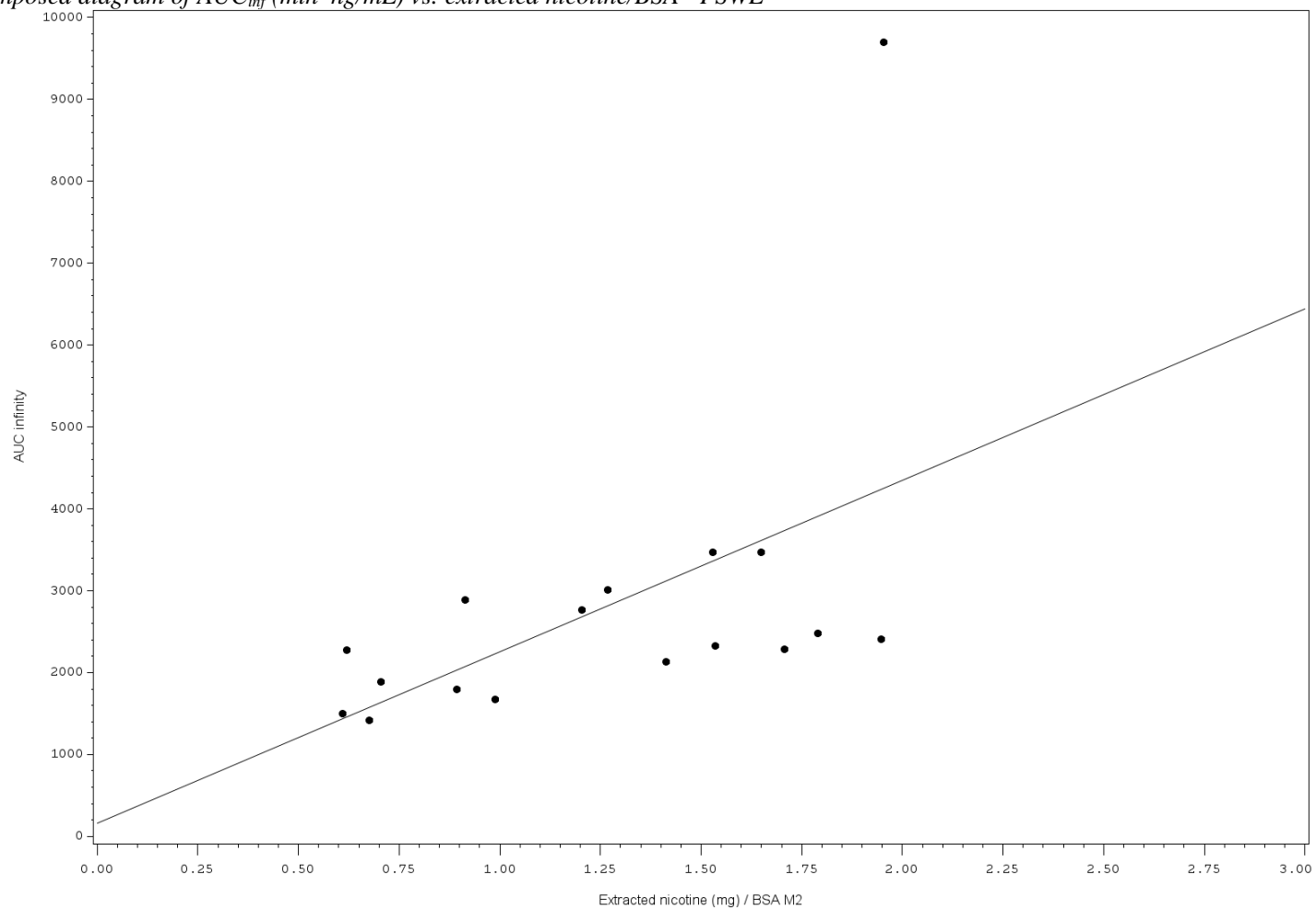
Figure 14.3-5 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine (mg) - ZSA6



Regression Equation:
AUC = 904.6275 + 785.6093*EXT_nic

RSQUARE=0.1929591638

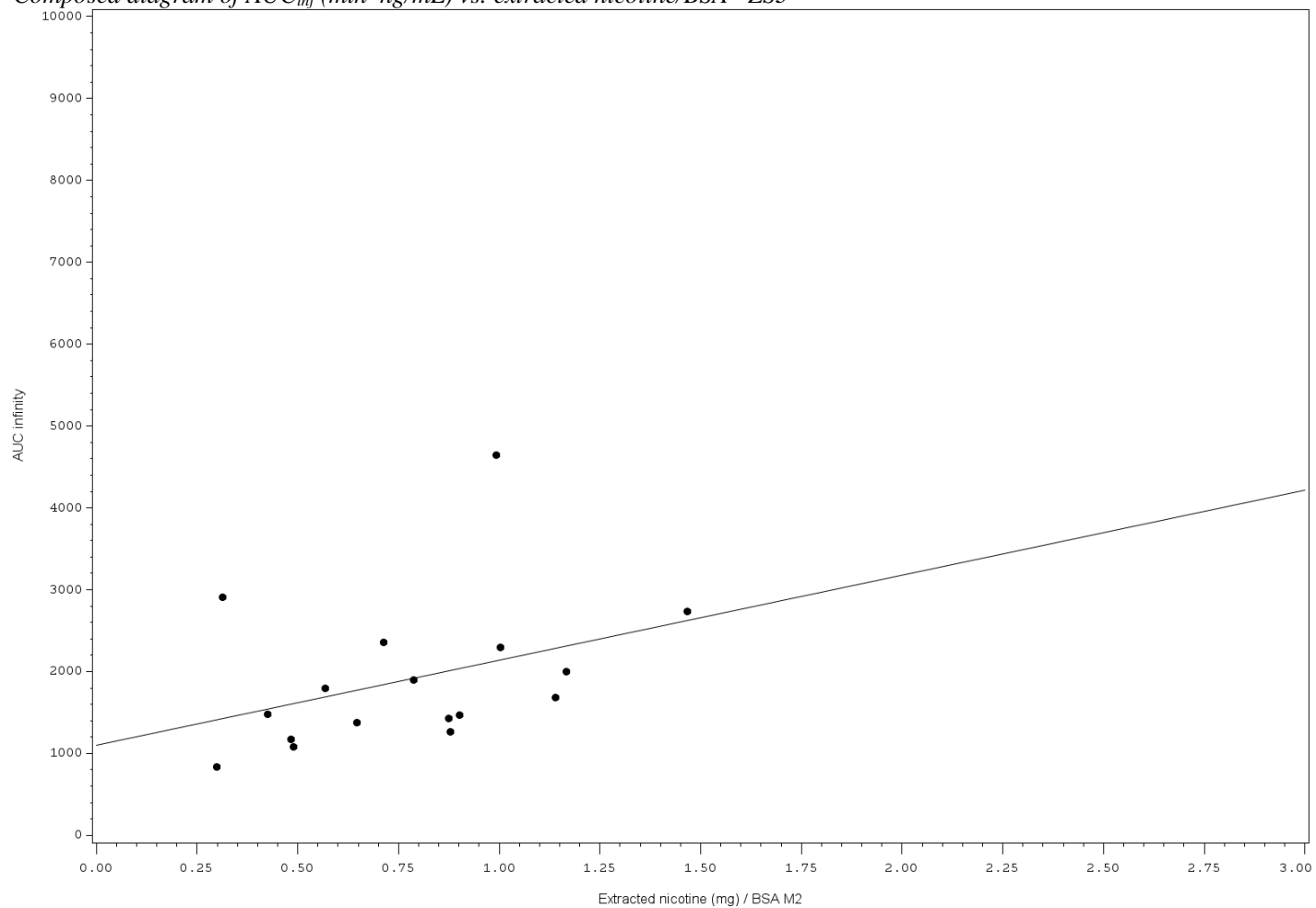
Figure 14.3-6 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine/BSA - PSWL



Regression Equation:
 $AUC = 158.9928 + 2092.629 \cdot bsa_ext_mg$

RSQUARE=0.2752490906

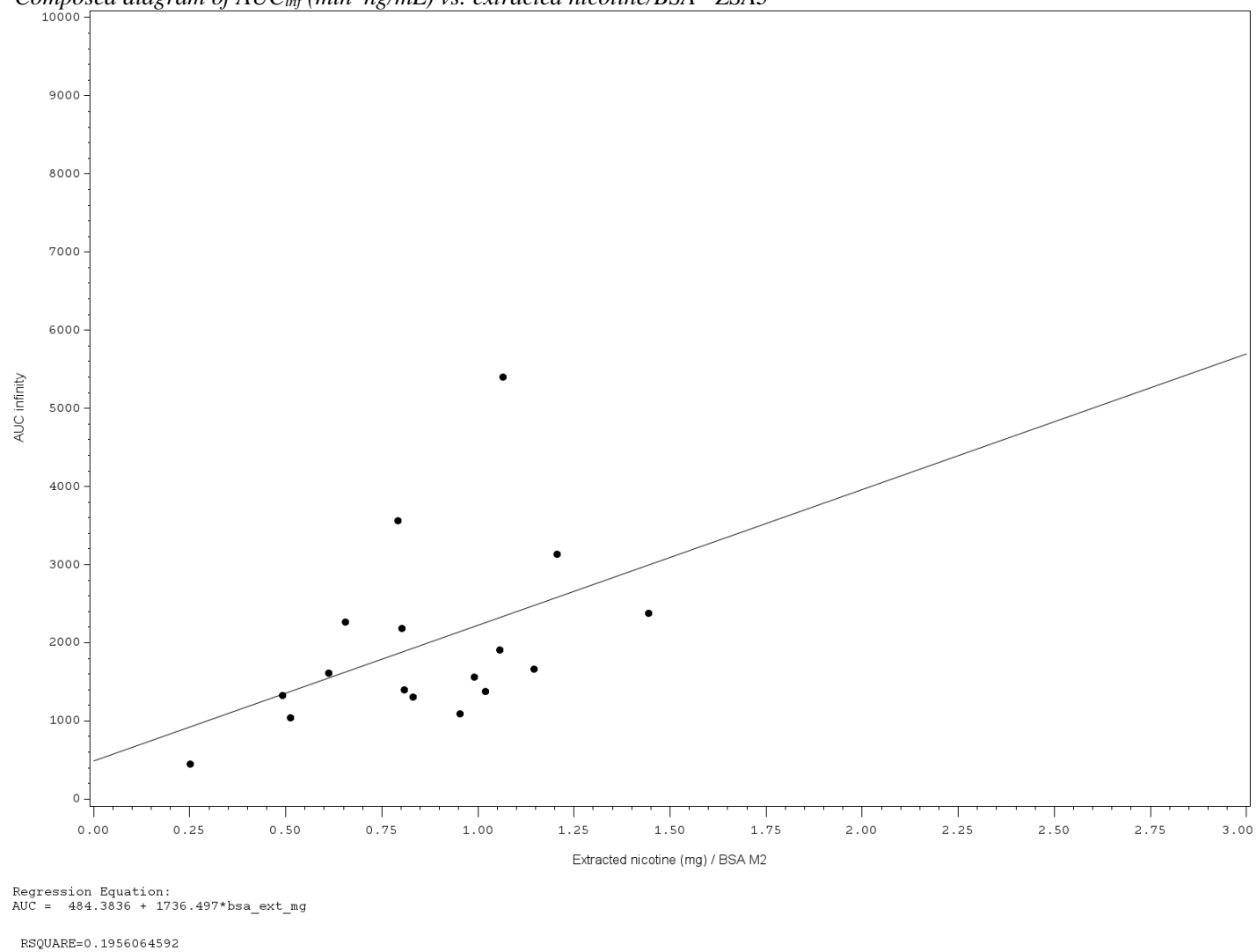
Figure 14.3-7 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine/BSA - ZS3



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Figure 14.3-8 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine/BSA - ZSA3



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Figure 14.3-9 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine/BSA - ZS6

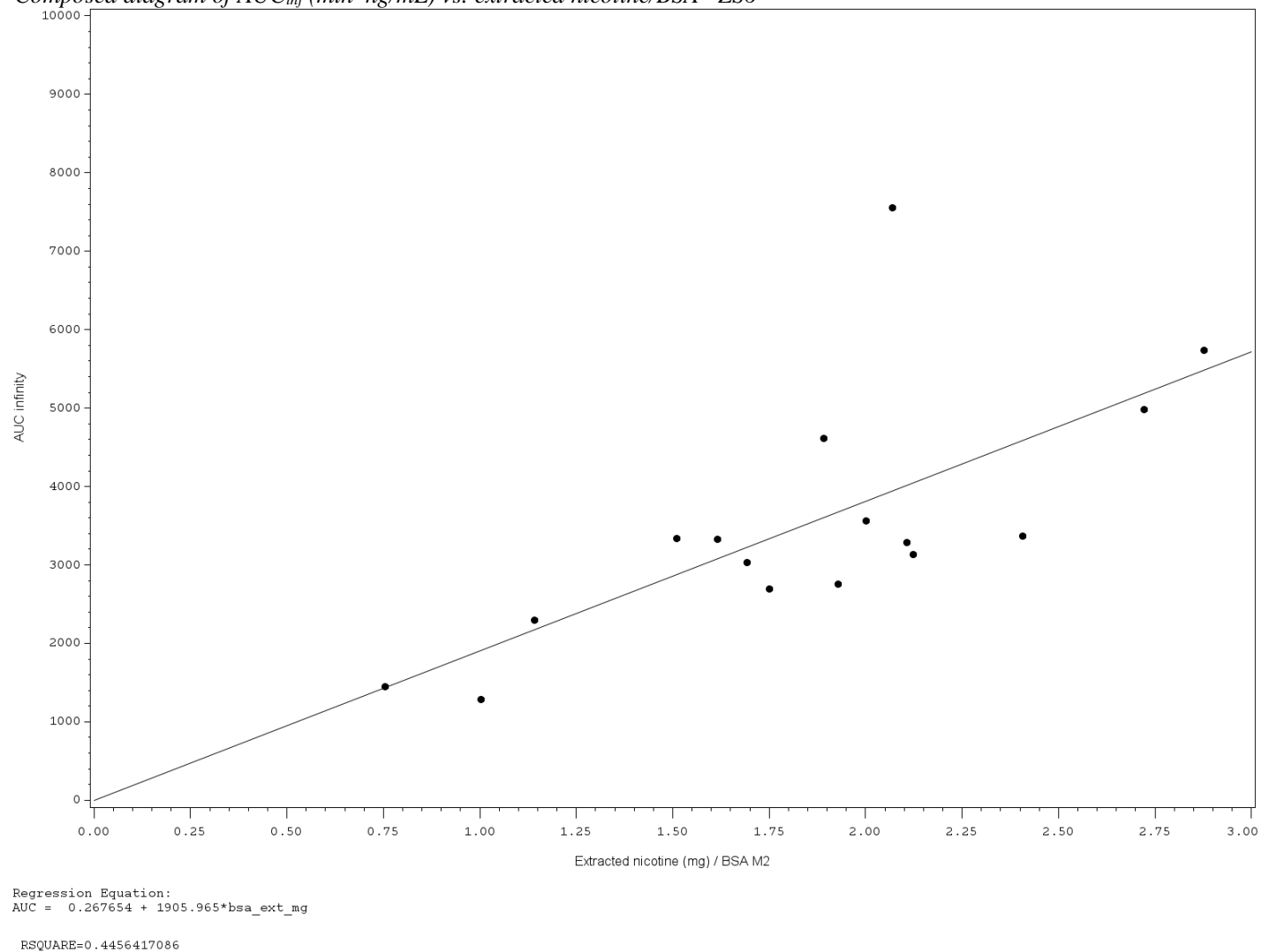
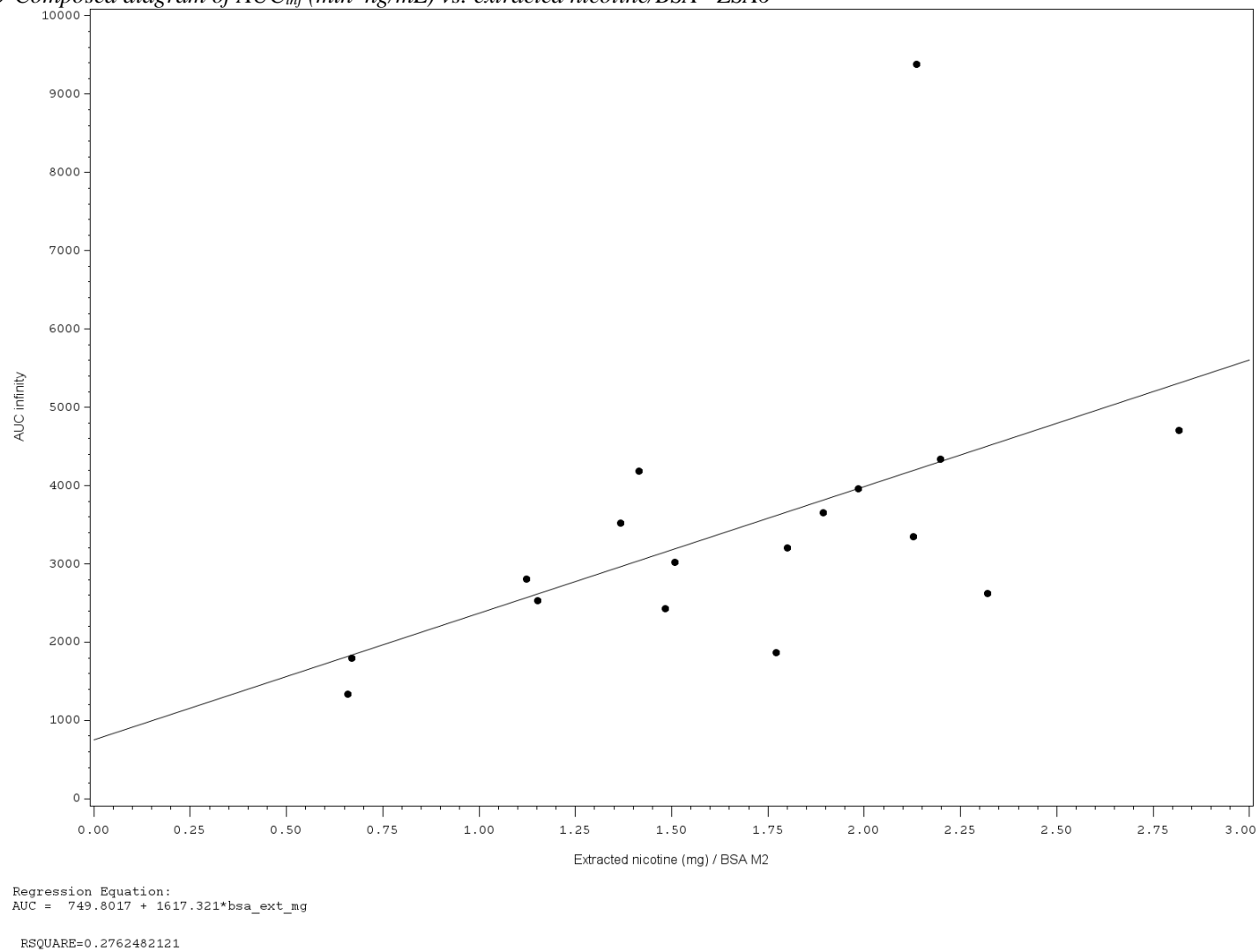


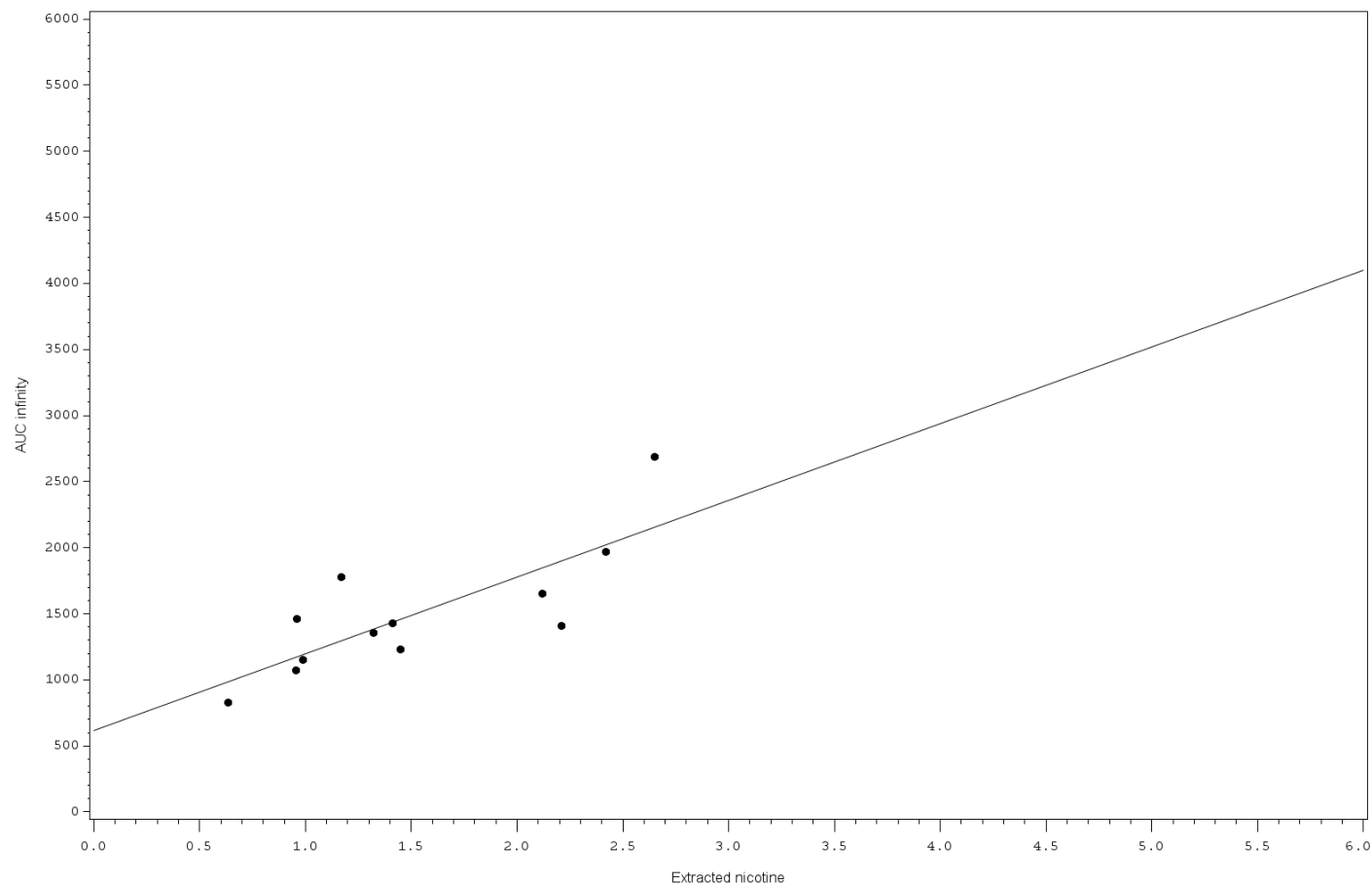
Figure 14.3-10 Composed diagram of AUC_{inf} (min*ng/mL) vs. extracted nicotine/BSA - ZSA6



14.3.2.3 Correlations AUC_{inf} and extracted nicotine (non-baseline adjusted data, $N=12$)

Figure 14.3-11 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 3 mg

Figure 14.2.3.1.1 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 3 mg



Regression Equation:
 $AUC = 615.8379 + 580.7825 \cdot EXT_nic$

RSQUARE=0.6258420668

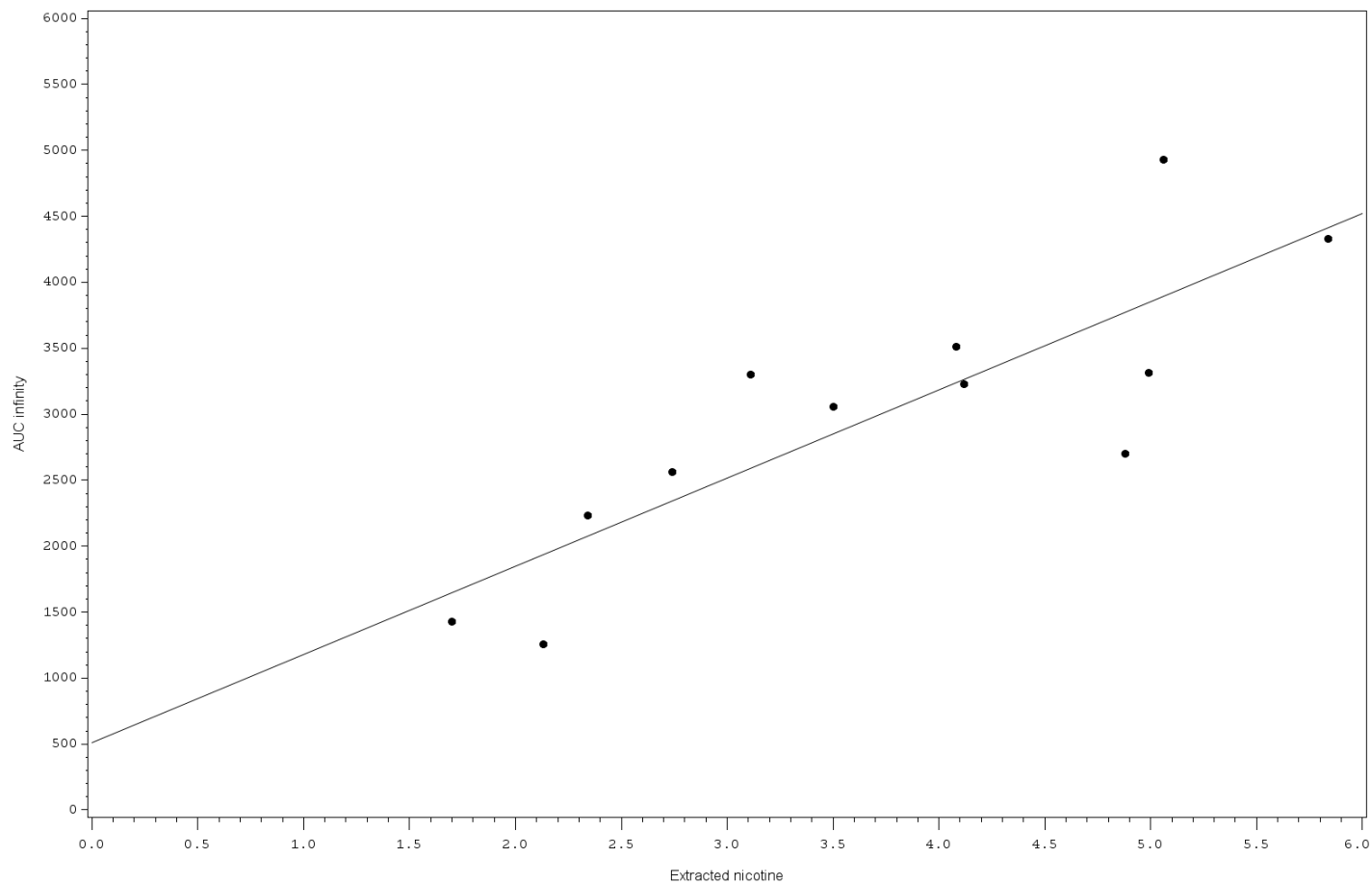
SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T12:03:37

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Figure 14.3-12 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 6 mg

Figure 14.2.3.1.2 Composed diagram of AUC inf (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 6 mg



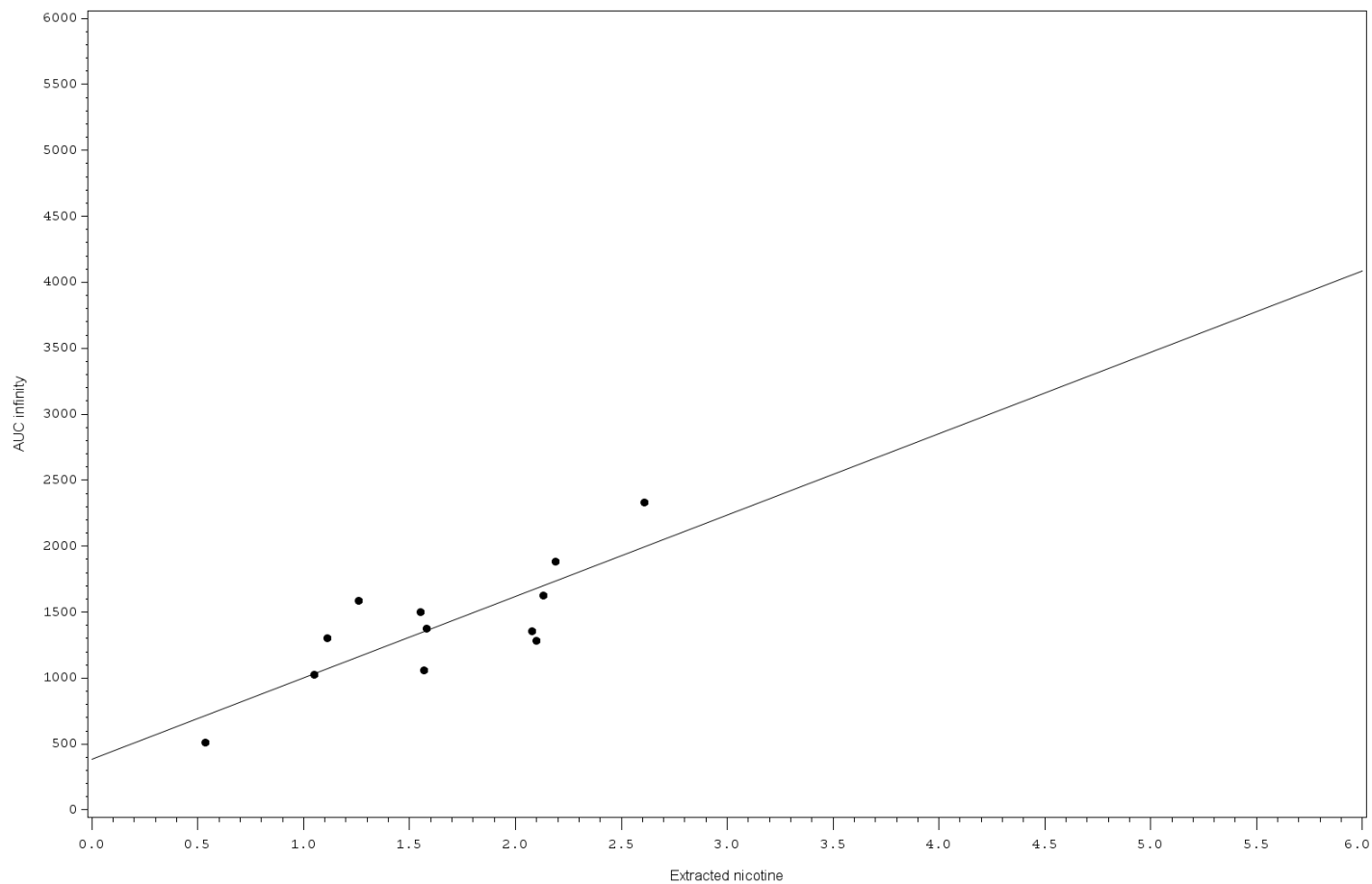
Regression Equation:
AUC = 513.0853 + 667.3331*EXT_nic

RSQUARE=0.6992168548

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T12:03:37

Figure 14.3-13 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 3 mg (alt. manu. proc.)

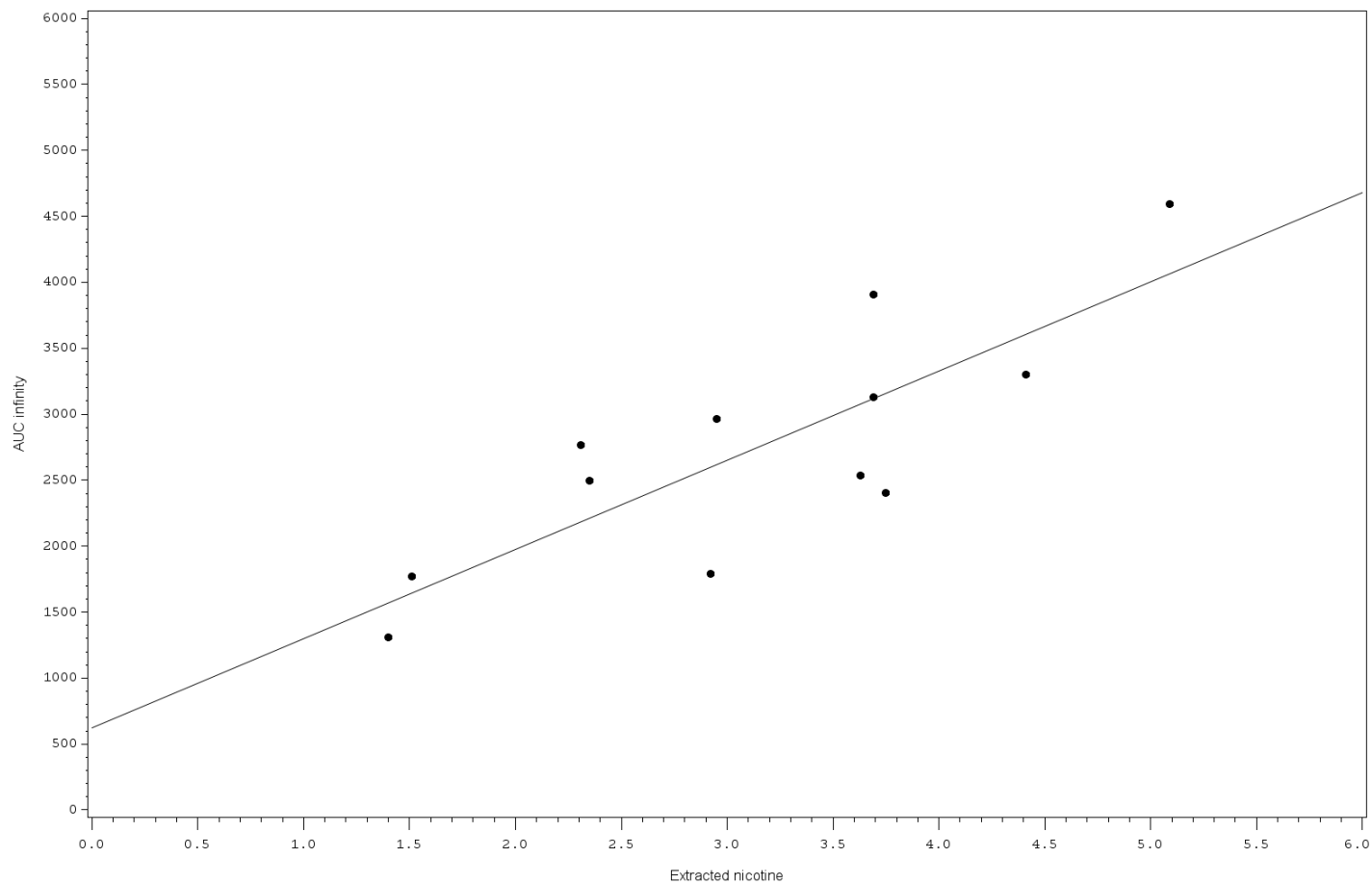
Figure 14.2.3.1.3 Composed diagram of AUC inf (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 3 mg (alt. manu. proc.)



SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T12:03:37

Figure 14.3-14 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 6 mg (alt. manu. proc.)

Figure 14.2.3.1.4 Composed diagram of AUC inf (min*ng/mL) versus extracted nicotine (mg) - ZYN Smooth 6 mg (alt. manu. proc.)



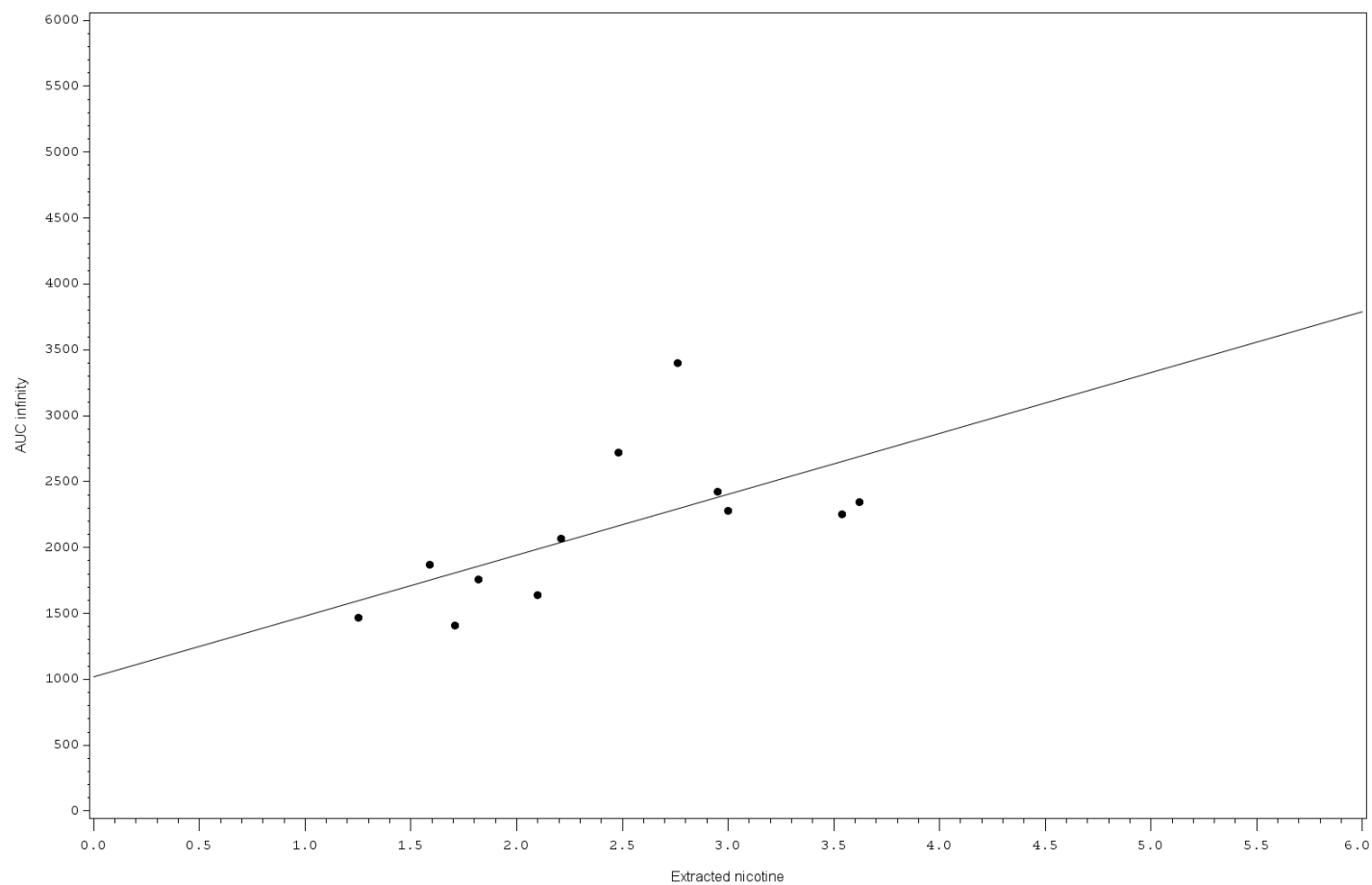
Regression Equation:
AUC = 624.895 + 675.6135*EXT_nic

RSQUARE=0.6664297838

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T12:03:37

Figure 14.3-15 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg) - Swedish portion snus PSWL 1.0 g (8 mg)

Figure 14.2.3.1.5 Composed diagram of AUC inf (min*ng/mL) versus extracted nicotine (mg) - Swedish portion snus PSWL 1.0 g (8 mg)

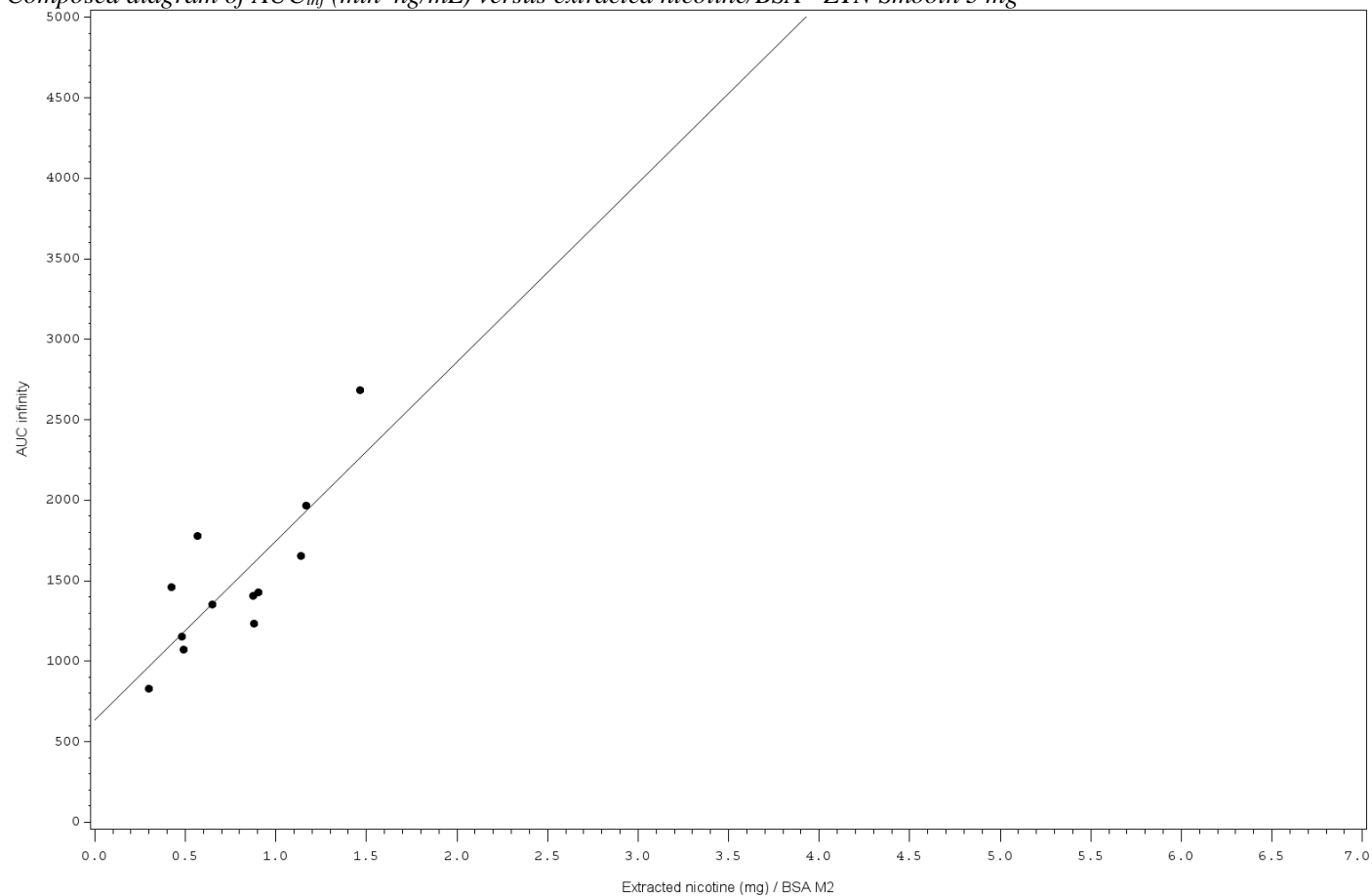


Regression Equation:
AUC = 1018.395 + 461.5807*EXT_nic

RSQUARE=0.3910718931

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T12:03:37

Figure 14.3-16 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA - ZYN Smooth 3 mg

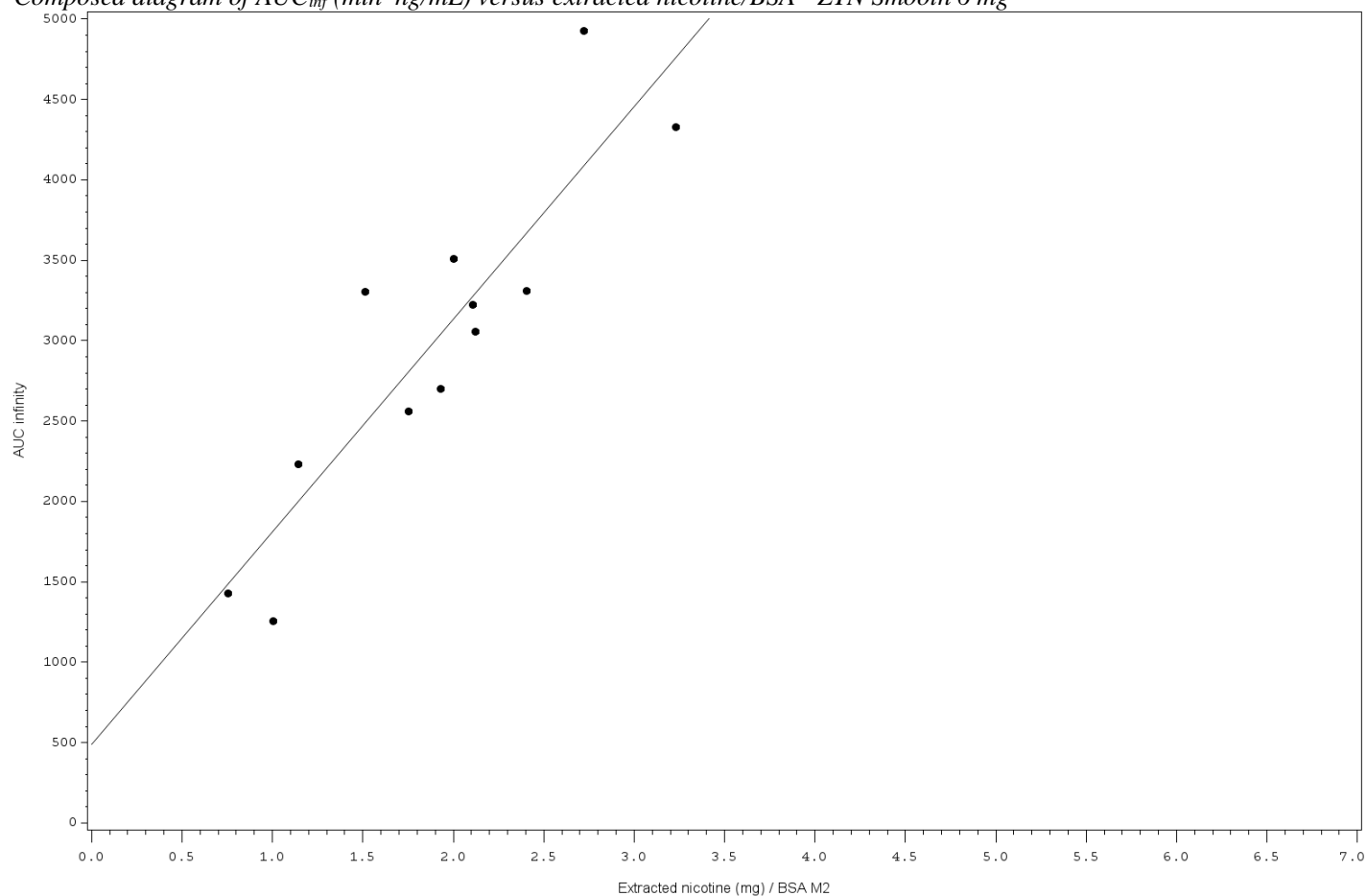


Regression Equation:
AUC = 635.8958 + 1111.543*bsa_ext_mg

RSQUARE=0.6258420668

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_bsa.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:45
With baseline adjustments

Figure 14.3-17 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA - ZYN Smooth 6 mg

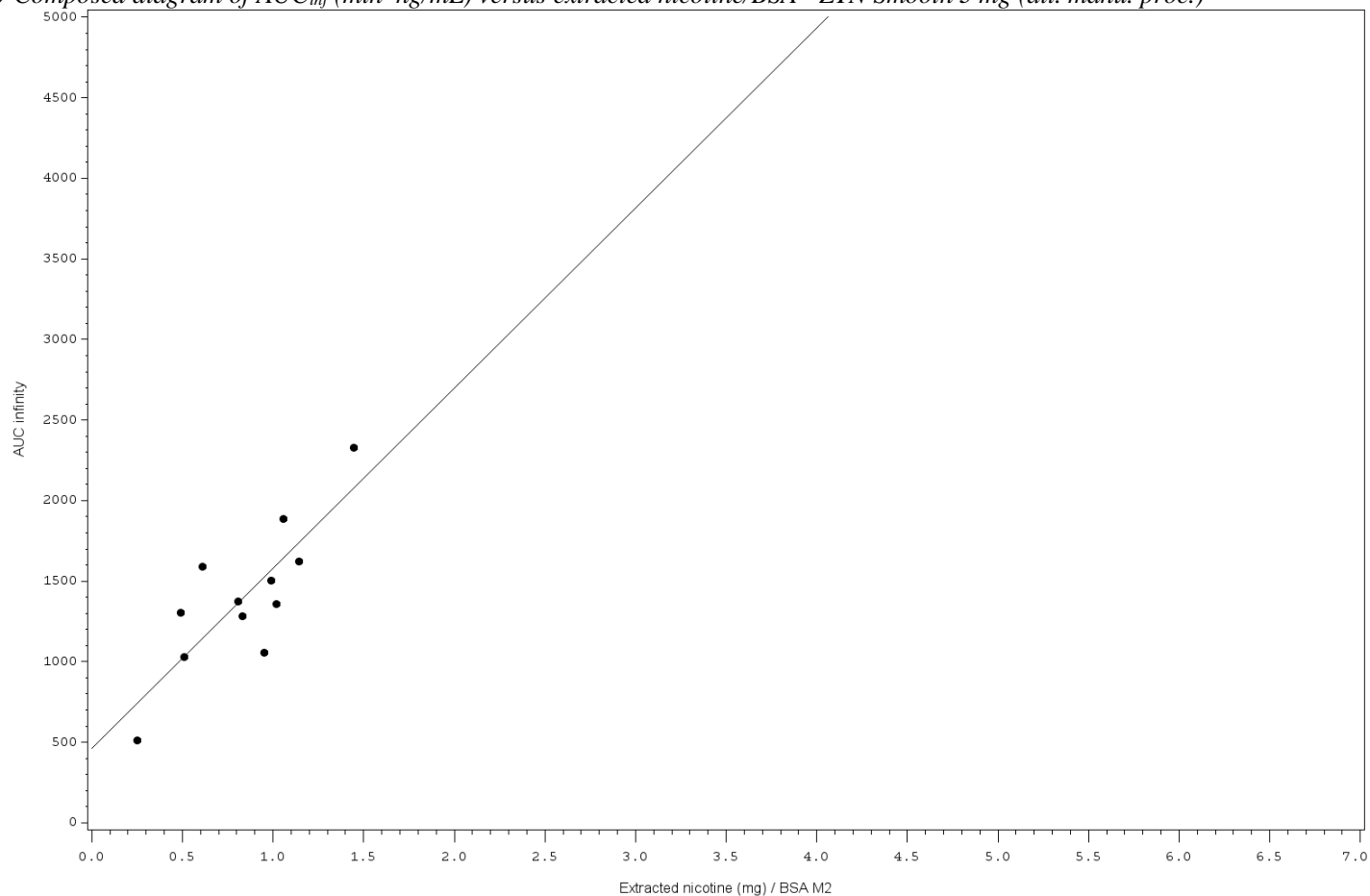


Regression Equation:
 $AUC = 487.2434 + 1322.741 \cdot bsa_ext_mg$

RSQUARE=0.6992168548

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_bsa.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:45
 With baseline adjustments

Figure 14.3-18 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA - ZYN Smooth 3 mg (alt. manu. proc.)

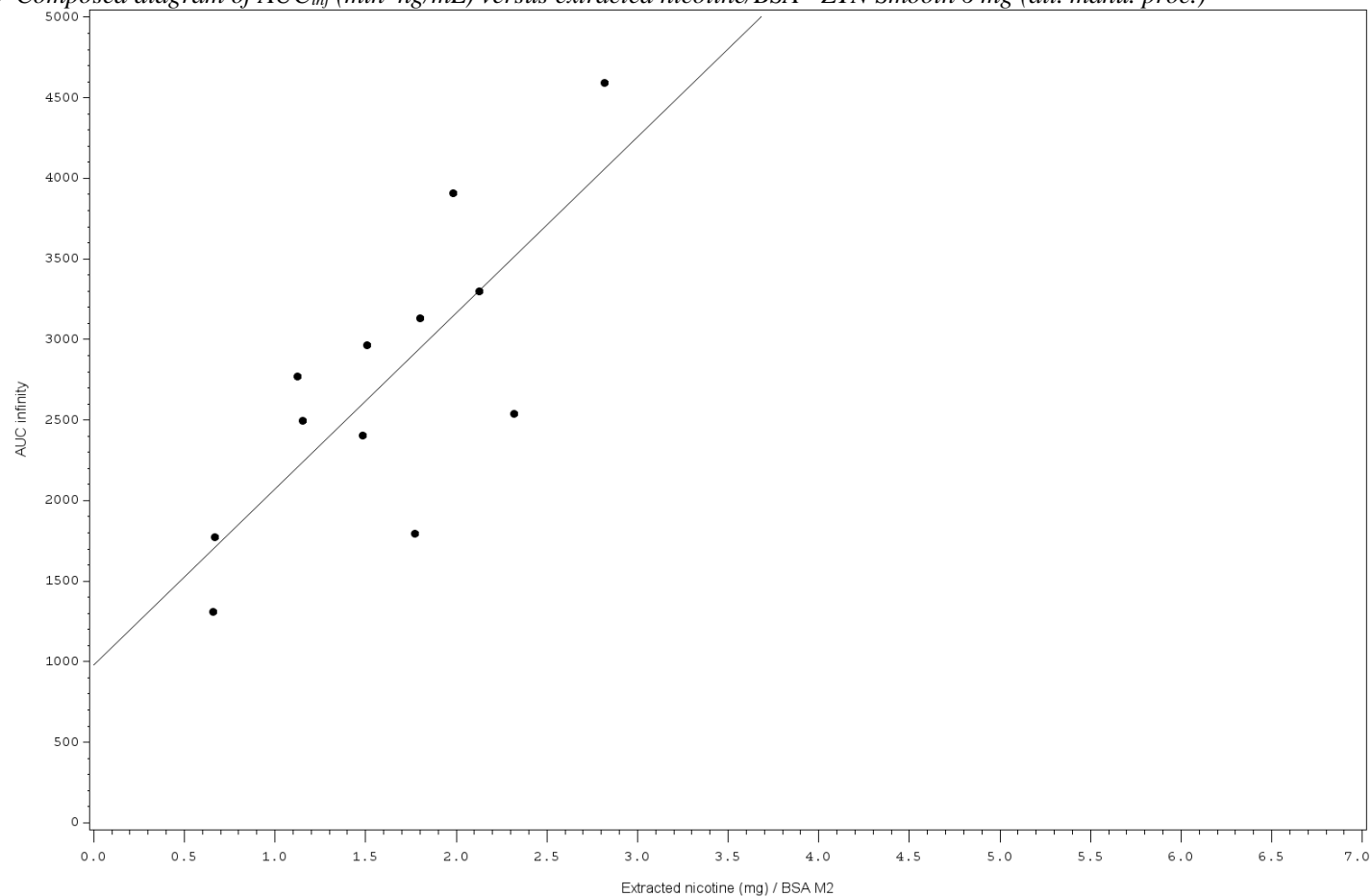


Regression Equation:
AUC = 461.6178 + 1117.01*bsa_ext_mg

RSQUARE=0.6531308854

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_bsa.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:45
With baseline adjustments

Figure 14.3-19 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA - ZYN Smooth 6 mg (alt. manu. proc.)

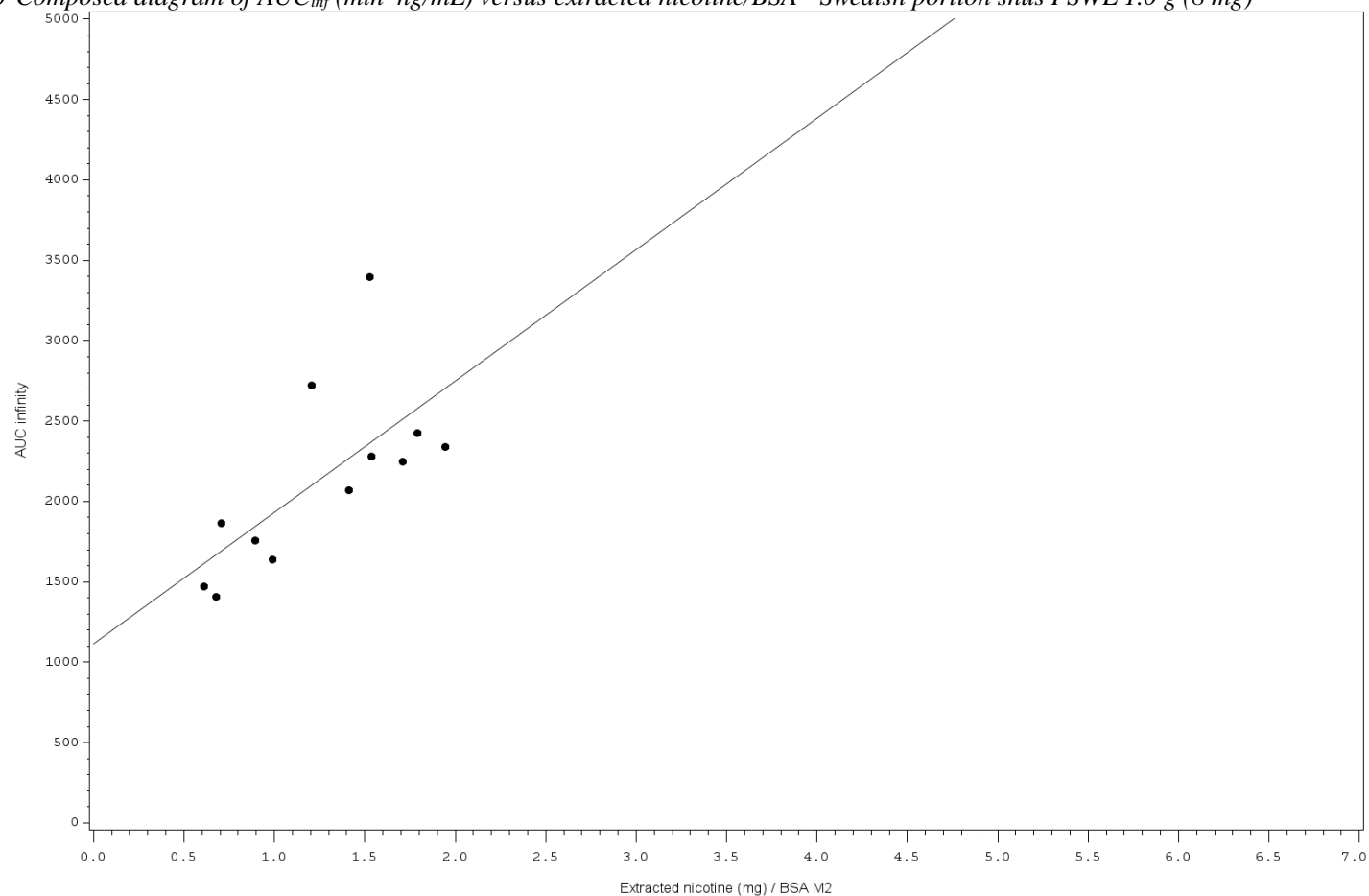


Regression Equation:
 $AUC = 981.2918 + 1091.71 * bsa_ext_mg$

RSQUARE=0.6664297838

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_bsa.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:45
 With baseline adjustments

Figure 14.3-20 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA - Swedish portion snus PSWL 1.0 g (8 mg)



Regression Equation:
 $AUC = 1114.17 + 817.0209 \cdot bsa_ext_mg$

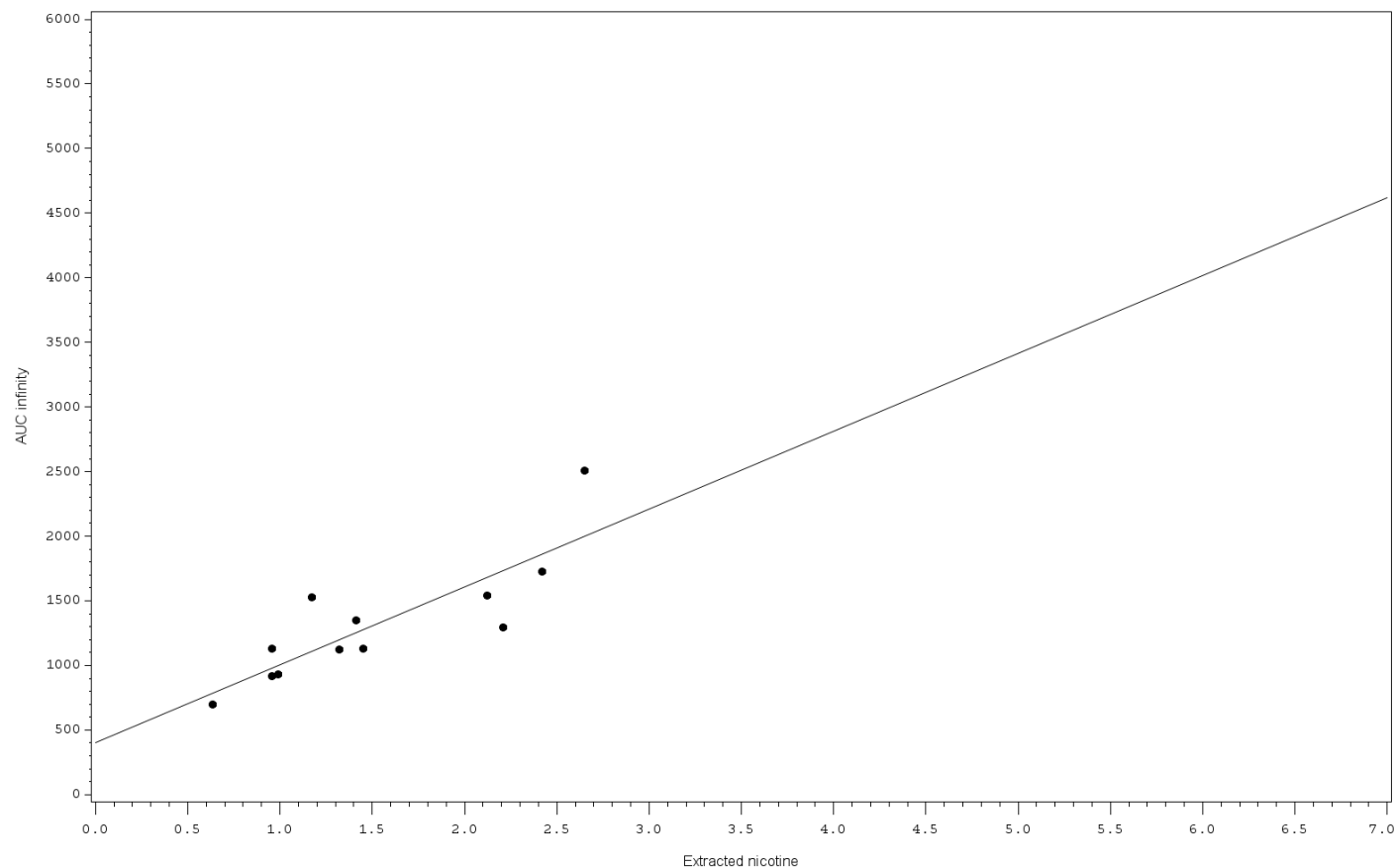
RSQUARE=0.3910718931

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_bsa.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:45
 With baseline adjustments

14.3.2.4 Correlations AUC_{inf} and extracted nicotine (baseline adjusted data, $N=12$)

Figure 14.3-21 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg), with baseline adjustment - ZYN Smooth 3 mg

Figure 14.2.3.2.1 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg), with baseline adjustment - ZYN Smooth 3 mg



Regression Equation:
AUC = 405.048 + 602.121*EXT_nic

RSQUARE=0.7028464508

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:45:22
With baseline adjustments

Figure 14.3-22 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg), with baseline adjustment - ZYN Smooth 6 mg

Figure 14.2.3.2.2 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg), with baseline adjustment - ZYN Smooth 6 mg

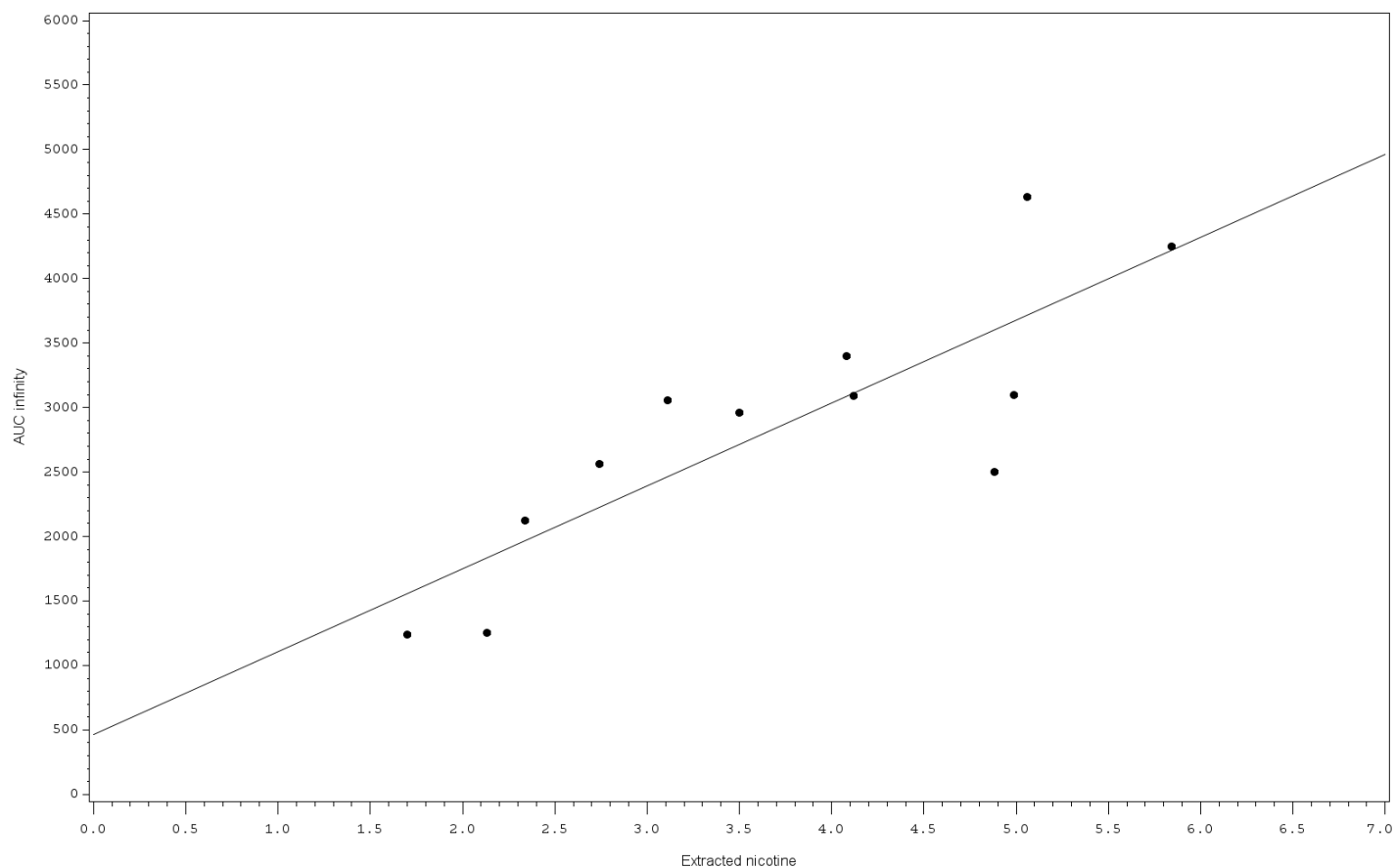
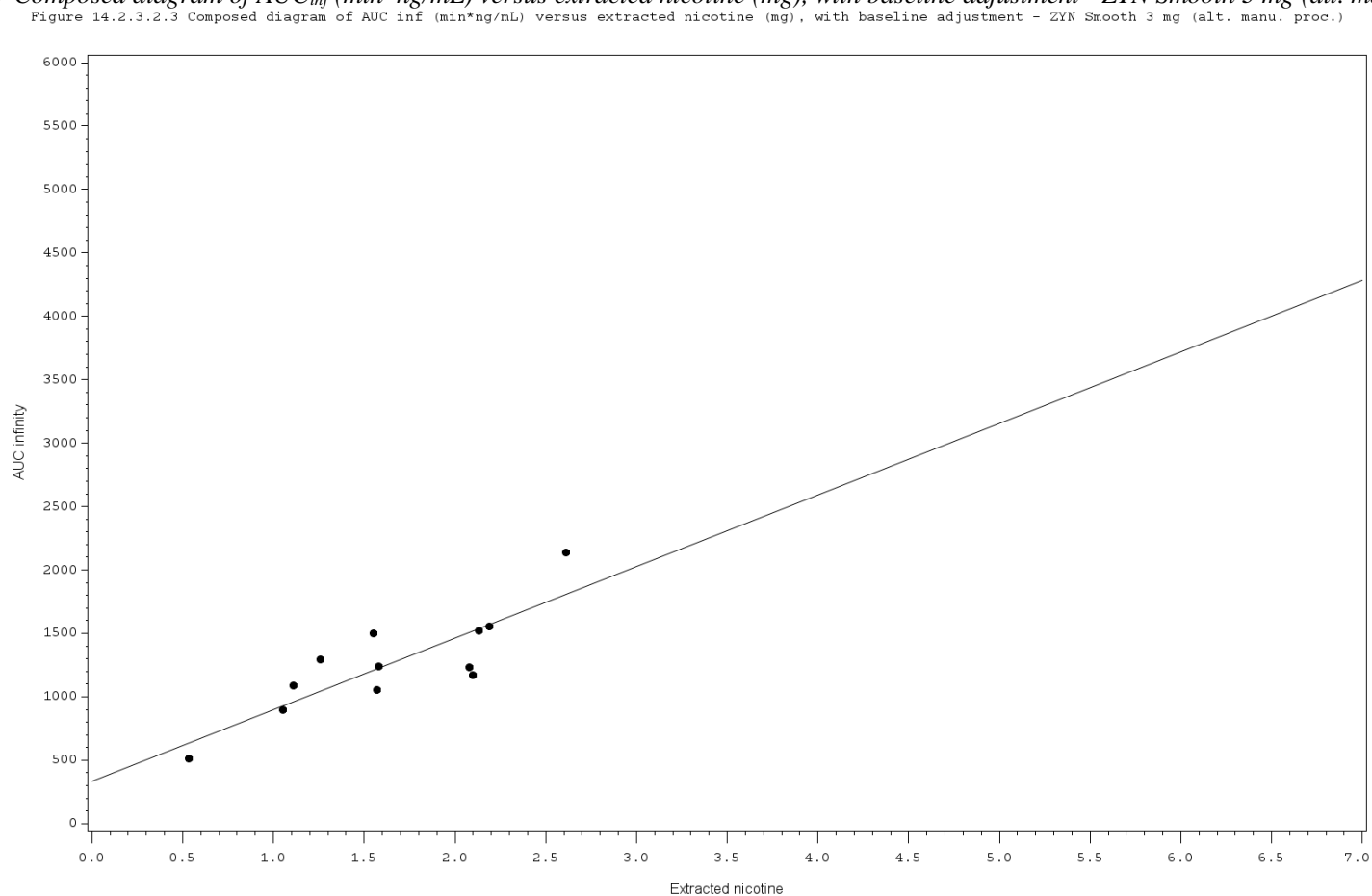


Figure 14.3-23 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg), with baseline adjustment - ZYN Smooth 3 mg (alt. manu. proc.)

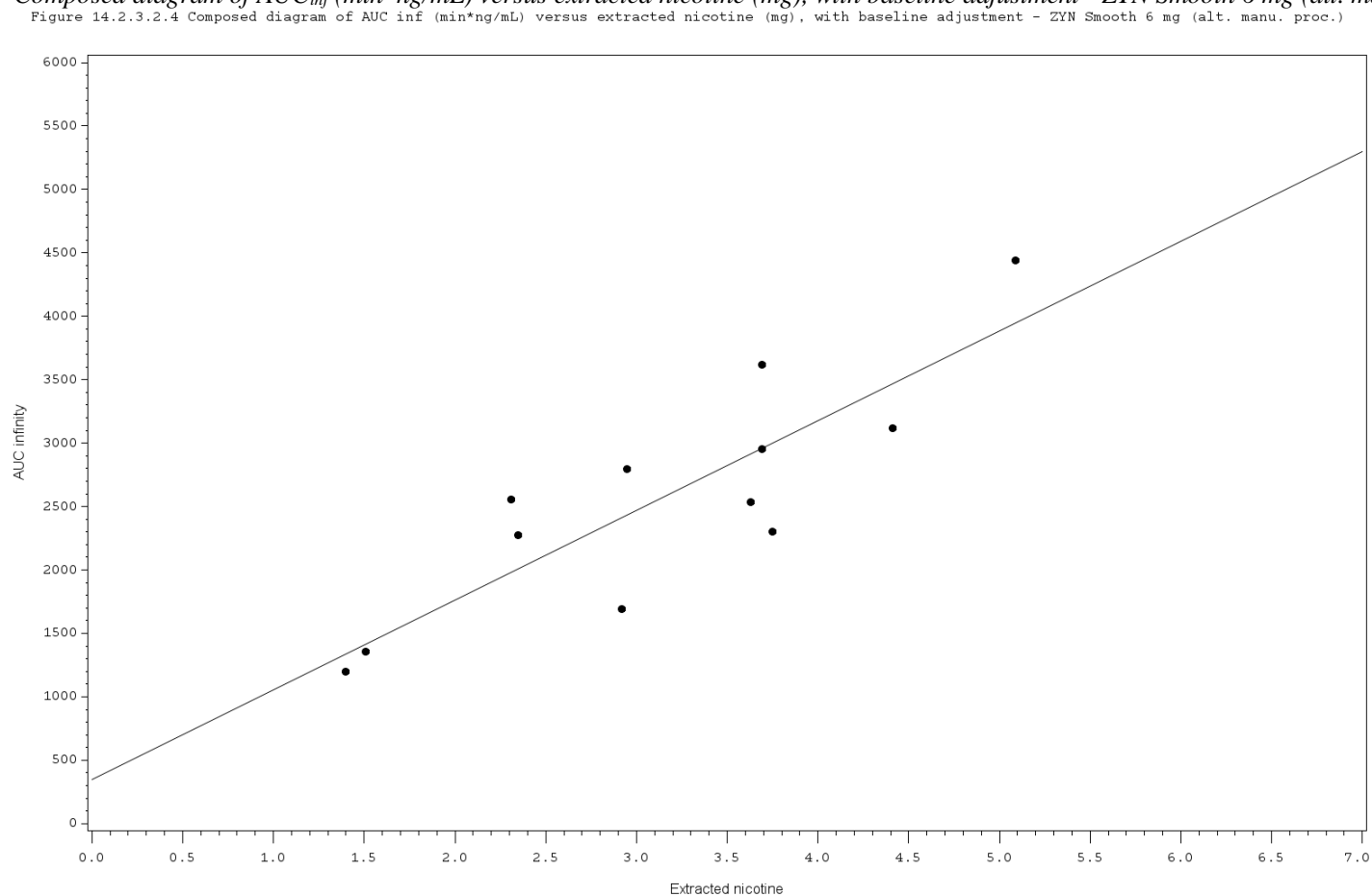


Regression Equation:
 $AUC = 337.0948 + 563.8957 \cdot EXT_nic$

RSQUARE=0.7077523409

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:45:22
 With baseline adjustments

Figure 14.3-24 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg), with baseline adjustment - ZYN Smooth 6 mg (alt. manu. proc.)



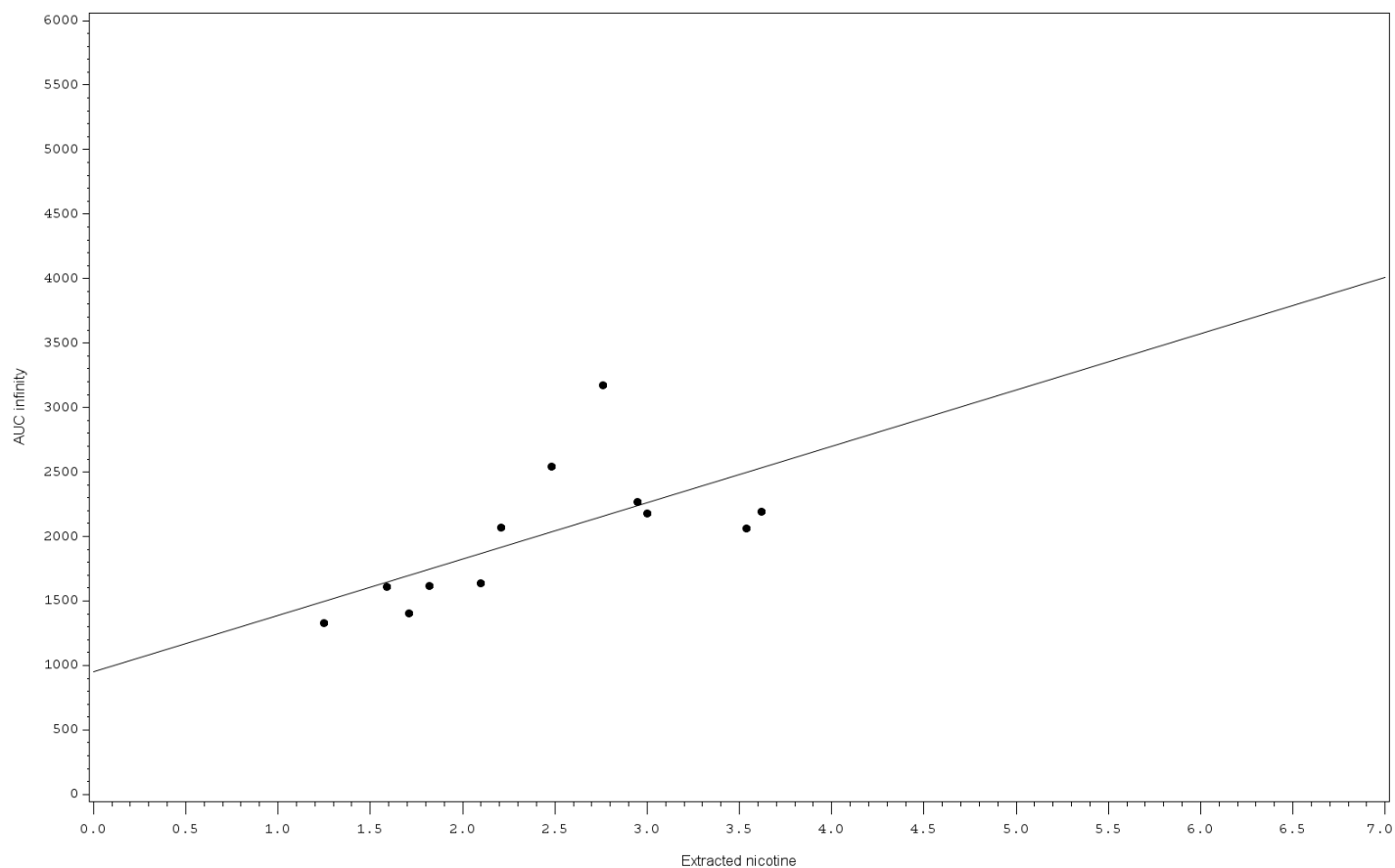
Regression Equation:
 $AUC = 348.0626 + 707.0618 \cdot EXT_nic$

RSQUARE=0.7319854192

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:45:22
 With baseline adjustments

Figure 14.3-25 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg) - Swedish portion snus PSWL 1.0 g (8 mg)

Figure 14.2.3.2.5 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine (mg), with baseline adjustment - Swedish portion snus PSWL 1.0 g (8 mg)

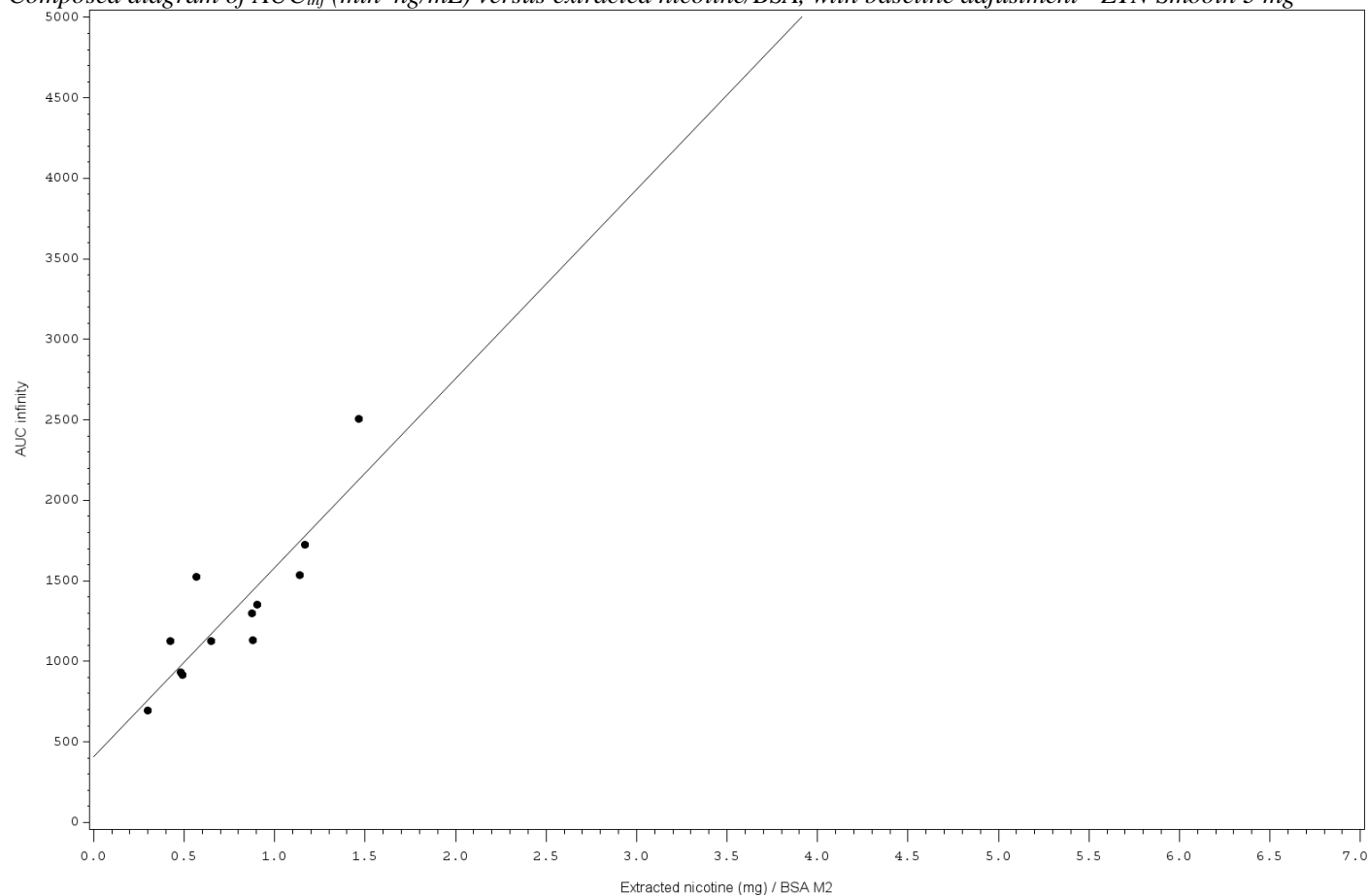


Regression Equation:
 $AUC = 951.2307 + 436.3275 \cdot EXT_nic$

RSQUARE=0.4064274753

SM17_03 Analysis of graphs, SAS program: graphs_auc_extracted_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:45:22
 With baseline adjustments

Figure 14.3-26 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA, with baseline adjustment - ZYN Smooth 3 mg

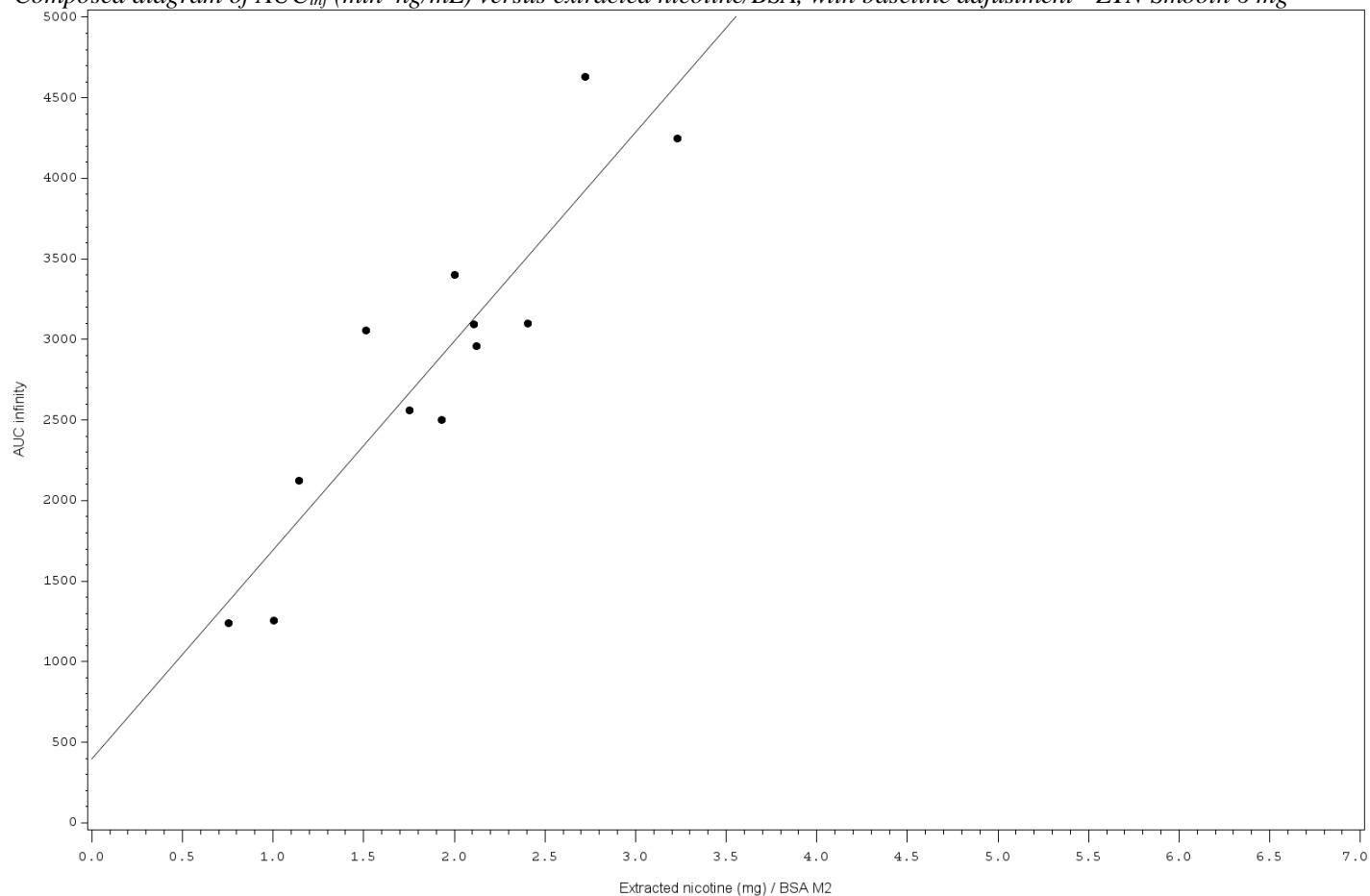


Regression Equation:
AUC = 409.3583 + 1173.567*bsa_ext_mg

RSQUARE=0.7028464508

SM17_03 Analysis of graphs, SAS program: graph_auc_extracted_bsa_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:20
With baseline adjustments

Figure 14.3-27 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA, with baseline adjustment - ZYN Smooth 6 mg

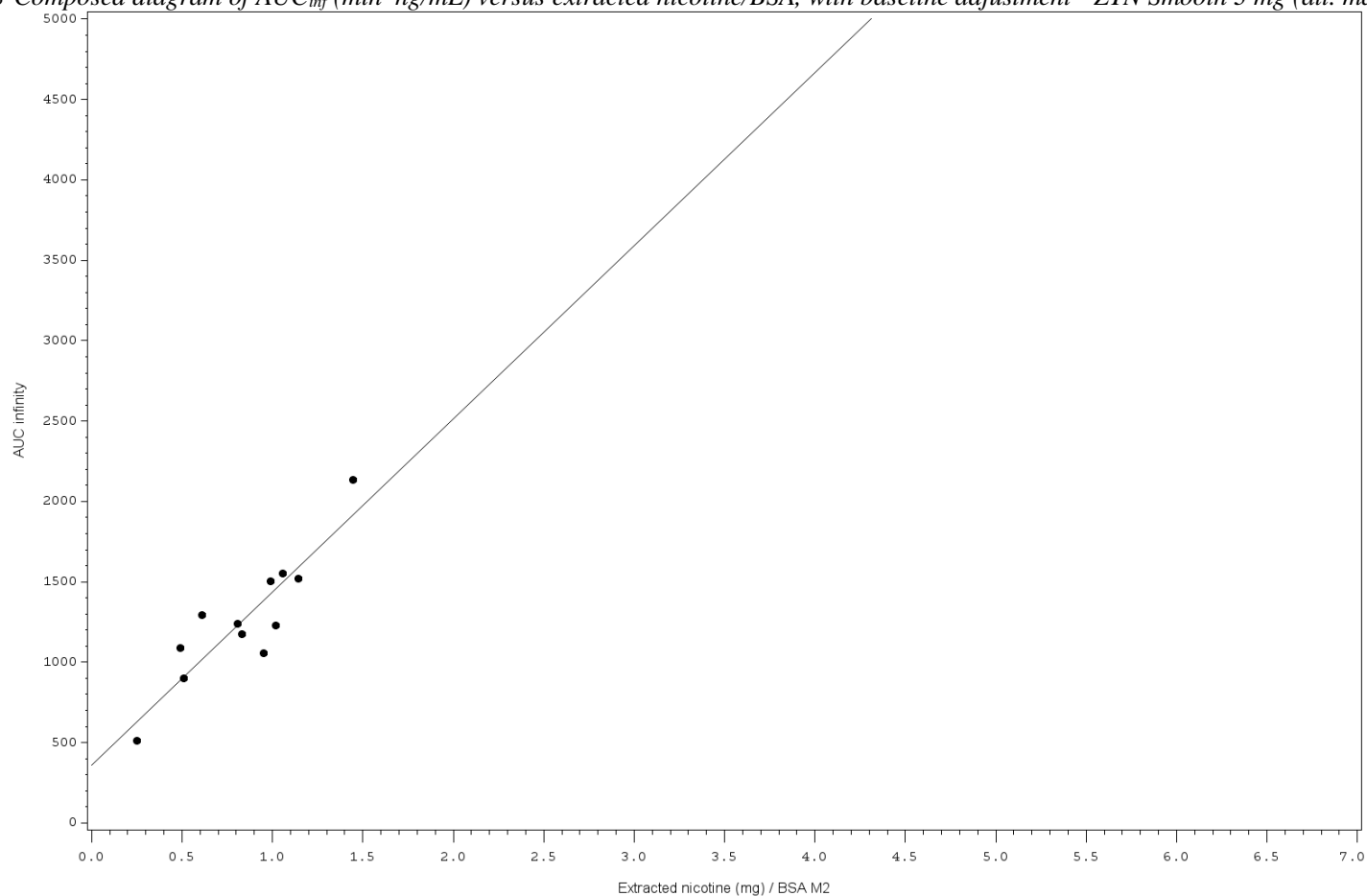


Regression Equation:
AUC = 397.8229 + 1296.043*bsa_ext_mg

RSQUARE=0.6983517738

SM17_03 Analysis of graphs, SAS program: graph_auc_extracted_bsa_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:20
With baseline adjustments

Figure 14.3-28 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA, with baseline adjustment - ZYN Smooth 3 mg (alt. manu. proc.)

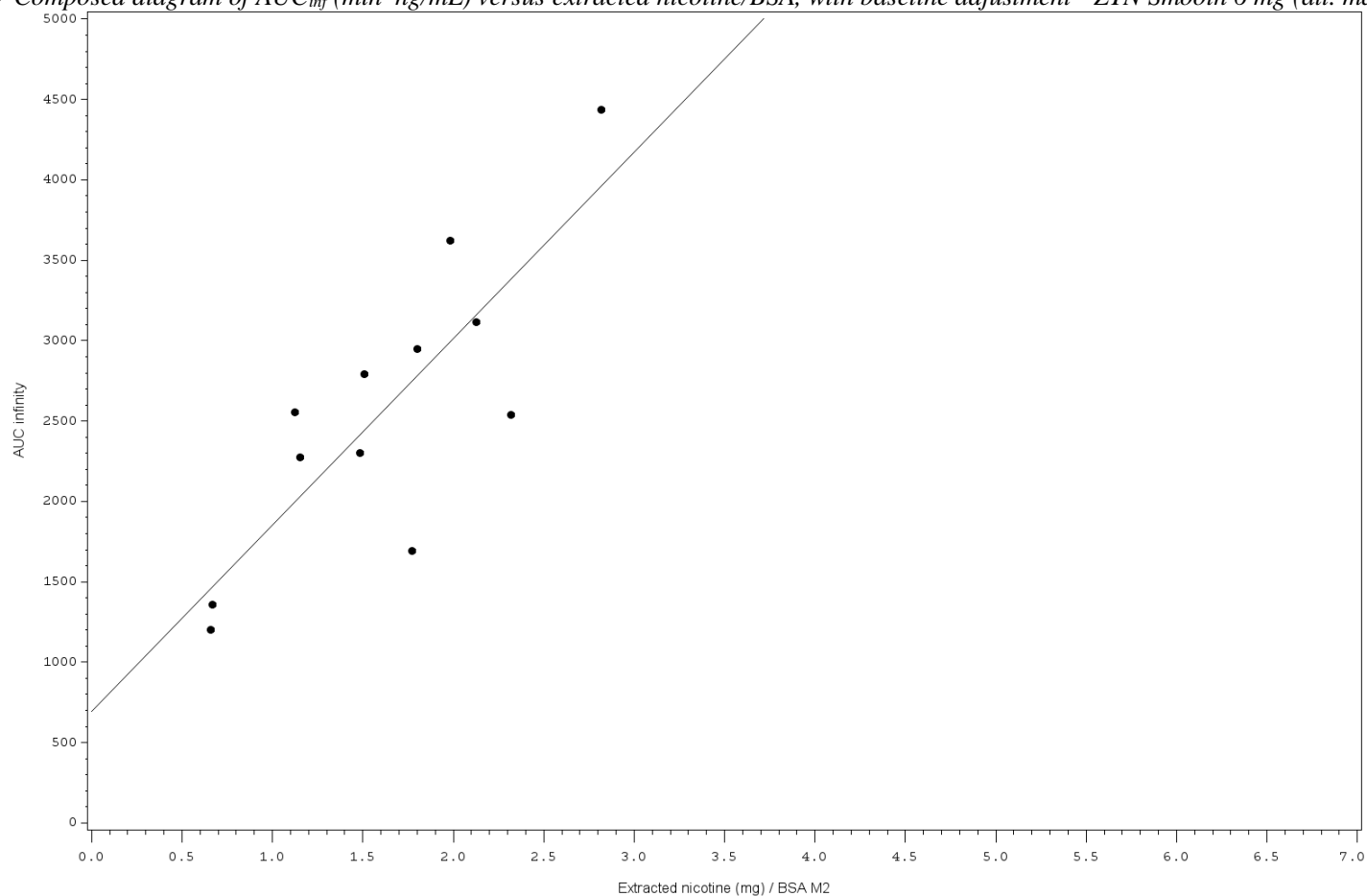


Regression Equation:
 $AUC = 357.6508 + 1077.421 \cdot bsa_ext_mg$

RSQUARE=0.7077523409

SM17_03 Analysis of graphs, SAS program: graph_auc_extracted_bsa_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:20
 With baseline adjustments

Figure 14.3-29 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA, with baseline adjustment - ZYN Smooth 6 mg (alt. manu. proc.)

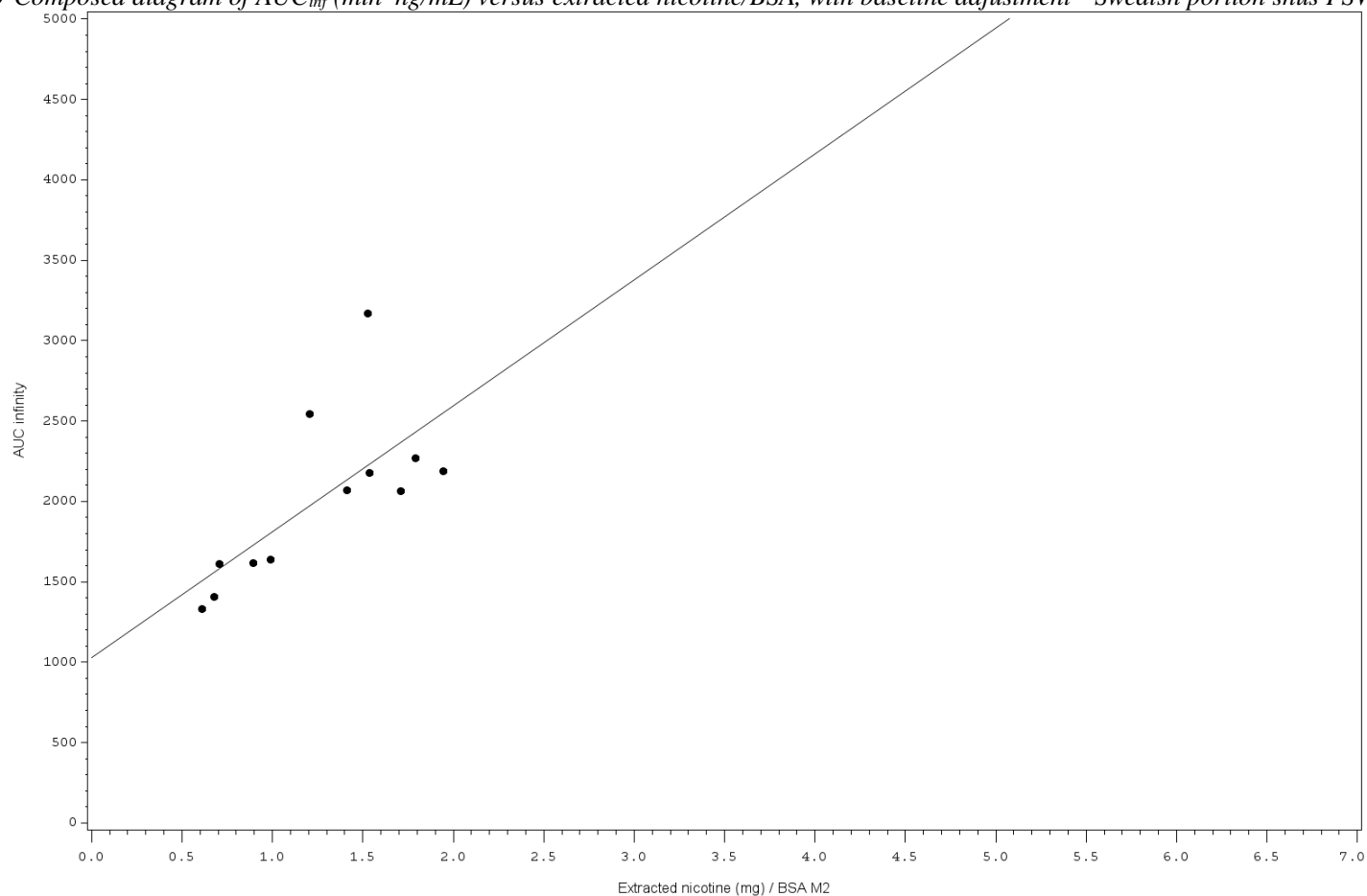


Regression Equation:
 $AUC = 696.0984 + 1157.949 \cdot bsa_ext_mg$

RSQUARE=0.7319854192

SM17_03 Analysis of graphs, SAS program: graph_auc_extracted_bsa_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:20
 With baseline adjustments

Figure 14.3-30 Composed diagram of AUC_{inf} (min*ng/mL) versus extracted nicotine/BSA, with baseline adjustment - Swedish portion snus PSWL 1.0 g (8 mg)



Regression Equation:
 $AUC = 1028.331 + 783.0736 * bsa_ext_mg$

RSQUARE=0.4064274753

SM17_03 Analysis of graphs, SAS program: graph_auc_extracted_bsa_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T14:44:20
 With baseline adjustments

14.3.2.5 Plasma concentration

Table 14.3-39 Difference in concentration (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg

Statistics	Time point in minutes	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	0	13 (4)	17 (0)	13 (4)	Student's t	0.4952
Mean (Std)	0	1.33 (0.66)	1.11 (0.56)	0.06 (0.33)	Signed Rank	0.5295
Median (min;max)	0	1.05 (0.59;3.06)	1.12 (0.54;2.71)	0.12 (-0.44;0.5)		
Q1, Q3 (IQR)	0	0.91 1.5 (0.59)	0.65 1.35 (0.7)	-0.24 0.35 (0.59)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.0805
Mean (Std)	5	2.36 (1.41)	1.74 (0.73)	0.61 (1.36)	Signed Rank	0.1202
Median (min;max)	5	1.94 (0.5;5.48)	1.66 (0.8;3.41)	0.38 (-1.69;3.38)		
Q1, Q3 (IQR)	5	1.2 3.51 (2.31)	1.16 1.99 (0.83)	-0.3 0.98 (1.28)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.0064
Mean (Std)	10	4.09 (1.75)	2.81 (0.91)	1.28 (1.68)	Signed Rank	0.0174
Median (min;max)	10	3.75 (0.74;7.38)	2.73 (1.37;4.72)	0.88 (-1.25;4.26)		
Q1, Q3 (IQR)	10	3.14 5.05 (1.91)	2.42 3.24 (0.82)	0.32 2.53 (2.21)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.0129
Mean (Std)	15	4.94 (1.93)	3.69 (1.16)	1.25 (1.85)	Signed Rank	0.0150
Median (min;max)	15	4.87 (1.19;9.09)	3.75 (2.02;5.5)	0.91 (-1.78;4.46)		
Q1, Q3 (IQR)	15	3.89 6.23 (2.34)	2.67 4.54 (1.87)	0.02 2.45 (2.43)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	0.0065
Mean (Std)	30	7.19 (2.59)	5.43 (1.61)	1.76 (2.32)	Signed Rank	0.0022
Median (min;max)	30	6.63 (2.52;12.8)	5.55 (3.04;8.56)	1.58 (-1.33;8.56)		
Q1, Q3 (IQR)	30	5.71 8.2 (2.49)	4.24 6.34 (2.1)	0.43 2.84 (2.41)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	0.0002
Mean (Std)	60	10.16 (3.01)	7.42 (2.7)	2.74 (2.4)	Signed Rank	0.0002
Median (min;max)	60	9.41 (4.79;17.5)	6.5 (3.3;13.8)	2.13 (-1.36;6.6)		
Q1, Q3 (IQR)	60	8.51 11.7 (3.19)	5.92 9.14 (3.22)	1.4 5.14 (3.74)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	90	9.63 (3.55)	6.42 (2.47)	3.2 (2.33)	Signed Rank	0.0001
Median (min;max)	90	9.48 (5.45;19.5)	5.97 (2.35;11.8)	3.6 (-0.19;7.9)		
Q1, Q3 (IQR)	90	6.73 10.7 (3.97)	5.04 7.2 (2.16)	1.6 4.58 (2.98)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	120	8.21 (3.53)	5.33 (2.18)	2.88 (2.25)	Signed Rank	0.0002
Median (min;max)	120	8.23 (4.21;19.3)	4.85 (2.08;10.7)	2.97 (-0.58;8.6)		
Q1, Q3 (IQR)	120	5.89 8.79 (2.9)	4.13 5.97 (1.84)	2.01 3.68 (1.67)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	0.0010
Mean (Std)	240	4.18 (2.77)	2.84 (1.56)	1.34 (1.39)	Signed Rank	<.0001
Median (min;max)	240	3.29 (1.8;14.1)	2.58 (1.15;8.01)	1.08 (-0.12;6.09)		
Q1, Q3 (IQR)	240	2.97 4.52 (1.55)	1.77 3.13 (1.36)	0.67 1.68 (1.01)		

Statistics	Time point in minutes	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	360	17 (0)	17 (0)	17 (0)	Student's t	0.0132
Mean (Std)	360	2.68 (2.22)	1.8 (1.04)	0.87 (1.29)	Signed Rank	<.0001
Median (min;max)	360	2.03 (1.29;10.8)	1.51 (0.8;5.14)	0.49 (0.04;5.66)		
Q1, Q3 (IQR)	360	1.55 2.86 (1.31)	1.1 2.28 (1.18)	0.29 0.89 (0.6)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-40 *Difference in concentration (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg (alt. manu. proc.)*

Statistics	Time point in minutes	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	0	13 (4)	13 (4)	12 (5)	Student's t	0.2397
Mean (Std)	0	1.33 (0.66)	1.68 (1.35)	-0.42 (1.17)	Signed Rank	0.3804
Median (min;max)	0	1.05 (0.59;3.06)	1.17 (0.57;5.41)	-0.07 (-3.6;0.91)		
Q1, Q3 (IQR)	0	0.91 1.5 (0.59)	0.73 2.15 (1.42)	-0.67 0.23 (0.9)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.2901
Mean (Std)	5	2.36 (1.41)	1.93 (1.22)	0.43 (1.61)	Signed Rank	0.1901
Median (min;max)	5	1.94 (0.5;5.48)	1.8 (0.63;5.48)	0.41 (-3.7;3.55)		
Q1, Q3 (IQR)	5	1.2 3.51 (2.31)	0.91 2.51 (1.6)	-0.13 1.21 (1.34)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.1015
Mean (Std)	10	4.09 (1.75)	3.18 (1.82)	0.91 (2.17)	Signed Rank	0.0448
Median (min;max)	10	3.75 (0.74;7.38)	2.69 (1.19;7.96)	1.05 (-4.82;4.47)		
Q1, Q3 (IQR)	10	3.14 5.05 (1.91)	1.67 3.73 (2.06)	0.3 2.07 (1.77)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.0984
Mean (Std)	15	4.94 (1.93)	3.86 (2.15)	1.08 (2.54)	Signed Rank	0.0624
Median (min;max)	15	4.87 (1.19;9.09)	3.44 (1.44;9.13)	0.99 (-4.81;5.65)		
Q1, Q3 (IQR)	15	3.89 6.23 (2.34)	2.34 4.28 (1.94)	-0.05 2.57 (2.62)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	0.0424
Mean (Std)	30	7.19 (2.59)	5.51 (2.81)	1.68 (3.14)	Signed Rank	0.0267
Median (min;max)	30	6.63 (2.52;12.8)	4.74 (2;11.8)	1.34 (-4.57;8.09)		
Q1, Q3 (IQR)	30	5.71 8.2 (2.49)	3.65 6.9 (3.25)	0.48 3.46 (2.98)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	0.0025
Mean (Std)	60	10.16 (3.01)	7.77 (2.81)	2.39 (2.75)	Signed Rank	0.0056
Median (min;max)	60	9.41 (4.79;17.5)	7.48 (2.17;12.1)	2.26 (-3.06;6.8)		
Q1, Q3 (IQR)	60	8.51 11.7 (3.19)	6.02 9.76 (3.74)	1.48 3.9 (2.42)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	0.0001
Mean (Std)	90	9.63 (3.55)	6.73 (2.43)	2.9 (2.41)	Signed Rank	0.0001
Median (min;max)	90	9.48 (5.45;19.5)	6.4 (1.81;11.4)	2.56 (-1.22;8.1)		
Q1, Q3 (IQR)	90	6.73 10.7 (3.97)	5.37 8.15 (2.78)	1.27 4.45 (3.18)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	0.0002
Mean (Std)	120	8.21 (3.53)	5.65 (2.3)	2.56 (2.25)	Signed Rank	0.0002
Median (min;max)	120	8.23 (4.21;19.3)	5.32 (1.46;11)	2.17 (-0.96;8.3)		
Q1, Q3 (IQR)	120	5.89 8.79 (2.9)	4.23 6.37 (2.14)	1.24 3.69 (2.45)		

Statistics	Time point in minutes	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	0.0050
Mean (Std)	240	4.18 (2.77)	2.88 (1.62)	1.31 (1.66)	Signed Rank	0.0007
Median (min;max)	240	3.29 (1.8;14.1)	2.39 (0.69;7.34)	1.15 (-1.11;6.76)		
Q1, Q3 (IQR)	240	2.97 4.52 (1.55)	1.96 3.23 (1.27)	0.5 1.54 (1.04)		
n (nmiss)	360	17 (0)	16 (1)	16 (1)	Student's t	0.0146
Mean (Std)	360	2.68 (2.22)	1.99 (1.35)	0.78 (1.13)	Signed Rank	0.0004
Median (min;max)	360	2.03 (1.29;10.8)	1.45 (0.77;6.08)	0.53 (-0.4;4.72)		
Q1, Q3 (IQR)	360	1.55 2.86 (1.31)	1.19 2.41 (1.22)	0.32 0.83 (0.51)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-41 Difference in concentration (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg

Statistics	Time point in minutes	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	0	13 (4)	14 (3)	13 (4)	Student's t	0.8543
Mean (Std)	0	1.33 (0.66)	1.28 (0.76)	0.03 (0.61)	Signed Rank	0.6355
Median (min;max)	0	1.05 (0.59;3.06)	1.13 (0.59;3.27)	0.01 (-1.46;1.06)		
Q1, Q3 (IQR)	0	0.91 1.5 (0.59)	0.74 1.35 (0.61)	-0.25 0.3 (0.55)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.9279
Mean (Std)	5	2.36 (1.41)	2.33 (0.81)	0.03 (1.38)	Signed Rank	0.8536
Median (min;max)	5	1.94 (0.5;5.48)	2.39 (1.01;3.94)	-0.05 (-2.16;3.16)		
Q1, Q3 (IQR)	5	1.2 3.51 (2.31)	1.67 2.94 (1.27)	-0.7 0.5 (1.2)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.0341
Mean (Std)	10	4.09 (1.75)	5.47 (1.87)	-1.38 (2.45)	Signed Rank	0.0448
Median (min;max)	10	3.75 (0.74;7.38)	5.48 (2.44;8.75)	-1.12 (-5.98;3.09)		
Q1, Q3 (IQR)	10	3.14 5.05 (1.91)	3.97 6.72 (2.75)	-3.55 0.55 (4.1)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.0005
Mean (Std)	15	4.94 (1.93)	7.07 (2.12)	-2.13 (2.02)	Signed Rank	0.0007
Median (min;max)	15	4.87 (1.19;9.09)	6.72 (3.8;11.6)	-1.85 (-5.78;1.41)		
Q1, Q3 (IQR)	15	3.89 6.23 (2.34)	5.69 8.81 (3.12)	-3.32 -0.92 (2.4)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	0.0020
Mean (Std)	30	7.19 (2.59)	10.11 (3.14)	-2.92 (3.27)	Signed Rank	0.0021
Median (min;max)	30	6.63 (2.52;12.8)	9.64 (4.84;18.5)	-3.4 (-11.3;1.11)		
Q1, Q3 (IQR)	30	5.71 8.2 (2.49)	8.33 11.1 (2.77)	-4.17 0.3 (4.47)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	60	10.16 (3.01)	15.36 (5.19)	-5.21 (3.76)	Signed Rank	0.0002
Median (min;max)	60	9.41 (4.79;17.5)	15 (6.02;27.8)	-5.62 (-12.6;1.57)		
Q1, Q3 (IQR)	60	8.51 11.7 (3.19)	12.5 17.5 (5)	-7.09 -3.8 (3.29)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	0.0004
Mean (Std)	90	9.63 (3.55)	12.95 (4.32)	-3.32 (3.1)	Signed Rank	0.0013
Median (min;max)	90	9.48 (5.45;19.5)	13.4 (4.77;19.9)	-3.99 (-8.77;1.57)		
Q1, Q3 (IQR)	90	6.73 10.7 (3.97)	10.7 16.1 (5.4)	-5.3 0 (5.3)		

Statistics	Time point in minutes	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	0.0012
Mean (Std)	120	8.21 (3.53)	10.9 (4.08)	-2.69 (2.82)	Signed Rank	0.0017
Median (min;max)	120	8.23 (4.21;19.3)	11.2 (3.81;18)	-3.21 (-8.02;1.8)		
Q1, Q3 (IQR)	120	5.89 8.79 (2.9)	8.28 13.1 (4.82)	-4.58 -1.04 (3.54)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	0.0058
Mean (Std)	240	4.18 (2.77)	5.52 (2.76)	-1.34 (1.73)	Signed Rank	0.0056
Median (min;max)	240	3.29 (1.8;14.1)	5.13 (1.53;12.6)	-1.02 (-4.32;1.5)		
Q1, Q3 (IQR)	240	2.97 4.52 (1.55)	3.99 6.35 (2.36)	-2.11 -0.41 (1.7)		
n (nmiss)	360	17 (0)	17 (0)	17 (0)	Student's t	0.0725
Mean (Std)	360	2.68 (2.22)	3.24 (1.94)	-0.57 (1.21)	Signed Rank	0.0585
Median (min;max)	360	2.03 (1.29;10.8)	3.02 (0.94;8.55)	-0.45 (-2.87;2.25)		
Q1, Q3 (IQR)	360	1.55 2.86 (1.31)	2.25 3.31 (1.06)	-1.19 0.1 (1.29)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program: sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-42 Difference in concentration (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	Time point in minutes	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	0	13 (4)	15 (2)	13 (4)	Student's t	0.4467
Mean (Std)	0	1.33 (0.66)	1.34 (0.77)	-0.13 (0.61)	Signed Rank	0.3757
Median (min;max)	0	1.05 (0.59;3.06)	1 (0.51;3.26)	-0.27 (-1.45;1.13)		
Q1, Q3 (IQR)	0	0.91 1.5 (0.59)	0.88 1.77 (0.89)	-0.41 0.12 (0.53)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.1897
Mean (Std)	5	2.36 (1.41)	2.72 (1.2)	-0.36 (1.09)	Signed Rank	0.1454
Median (min;max)	5	1.94 (0.5;5.48)	2.69 (0.86;5.72)	-0.28 (-1.85;2.04)		
Q1, Q3 (IQR)	5	1.2 3.51 (2.31)	1.71 3.49 (1.78)	-1.21 0.05 (1.26)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.1222
Mean (Std)	10	4.09 (1.75)	4.8 (1.69)	-0.71 (1.79)	Signed Rank	0.1594
Median (min;max)	10	3.75 (0.74;7.38)	4.62 (1.76;7.07)	-0.41 (-3.62;1.84)		
Q1, Q3 (IQR)	10	3.14 5.05 (1.91)	3.56 6.12 (2.56)	-2.42 0.42 (2.84)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.0177
Mean (Std)	15	4.94 (1.93)	6.48 (2.35)	-1.54 (2.39)	Signed Rank	0.0267
Median (min;max)	15	4.87 (1.19;9.09)	6.84 (2.55;10.2)	-1.21 (-5.94;1.77)		
Q1, Q3 (IQR)	15	3.89 6.23 (2.34)	4.91 8.29 (3.38)	-3.4 0.27 (3.67)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	0.0492
Mean (Std)	30	7.19 (2.59)	8.9 (3.05)	-1.72 (3.32)	Signed Rank	0.0569
Median (min;max)	30	6.63 (2.52;12.8)	8.09 (4.37;15.9)	-1.46 (-7.39;5.08)		
Q1, Q3 (IQR)	30	5.71 8.2 (2.49)	7.64 10.5 (2.86)	-4.17 0.56 (4.73)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	0.0012
Mean (Std)	60	10.16 (3.01)	13.43 (4.48)	-3.28 (3.43)	Signed Rank	<.0001
Median (min;max)	60	9.41 (4.79;17.5)	12.8 (7.21;24)	-2.79 (-13.02;0.15)		
Q1, Q3 (IQR)	60	8.51 11.7 (3.19)	10.9 13.8 (2.9)	-4.5 -0.7 (3.8)		

Statistics	Time point in minutes	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	0.0007
Mean (Std)	90	9.63 (3.55)	12.18 (4.22)	-2.55 (2.51)	Signed Rank	0.0014
Median (min;max)	90	9.48 (5.45;19.5)	12.1 (5.16;21)	-3.05 (-6.57;1.46)		
Q1, Q3 (IQR)	90	6.73 10.7 (3.97)	9.44 14 (4.56)	-4.7 -0.6 (4.1)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	0.0015
Mean (Std)	120	8.21 (3.53)	10.27 (3.98)	-2.06 (2.22)	Signed Rank	0.0026
Median (min;max)	120	8.23 (4.21;19.3)	9.83 (3.75;19.9)	-2.54 (-5.47;1.4)		
Q1, Q3 (IQR)	120	5.89 8.79 (2.9)	8.05 10.9 (2.85)	-3.83 -0.5 (3.33)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	0.0035
Mean (Std)	240	4.18 (2.77)	5.18 (2.78)	-0.99 (1.2)	Signed Rank	0.0043
Median (min;max)	240	3.29 (1.8;14.1)	4.62 (1.58;14.1)	-1.18 (-2.78;1.48)		
Q1, Q3 (IQR)	240	2.97 4.52 (1.55)	3.94 5.88 (1.94)	-1.69 -0.03 (1.66)		
n (nmiss)	360	17 (0)	17 (0)	17 (0)	Student's t	0.0024
Mean (Std)	360	2.68 (2.22)	3.31 (2.19)	-0.63 (0.72)	Signed Rank	0.0025
Median (min;max)	360	2.03 (1.29;10.8)	2.99 (1.01;10.7)	-0.69 (-2.12;0.89)		
Q1, Q3 (IQR)	360	1.55 2.86 (1.31)	2.17 3.84 (1.67)	-1 -0.13 (0.87)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-43 Difference in concentration (ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	Time point in minutes	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	0	17 (0)	13 (4)	13 (4)	Student's t	0.2228
Mean (Std)	0	1.11 (0.56)	1.68 (1.35)	-0.42 (1.18)	Signed Rank	0.5530
Median (min;max)	0	1.12 (0.54;2.71)	1.17 (0.57;5.41)	-0.07 (-3.72;0.56)		
Q1, Q3 (IQR)	0	0.65 1.35 (0.7)	0.73 2.15 (1.42)	-0.4 0.34 (0.74)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.4930
Mean (Std)	5	1.74 (0.73)	1.93 (1.22)	-0.19 (1.09)	Signed Rank	0.7909
Median (min;max)	5	1.66 (0.8;3.41)	1.8 (0.63;5.48)	0.17 (-3.19;1.61)		
Q1, Q3 (IQR)	5	1.16 1.99 (0.83)	0.91 2.51 (1.6)	-0.18 0.23 (0.41)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.3248
Mean (Std)	10	2.81 (0.91)	3.18 (1.82)	-0.37 (1.49)	Signed Rank	0.6441
Median (min;max)	10	2.73 (1.37;4.72)	2.69 (1.19;7.96)	-0.06 (-3.72;2.11)		
Q1, Q3 (IQR)	10	2.42 3.24 (0.82)	1.67 3.73 (2.06)	-0.55 0.46 (1.01)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.6778
Mean (Std)	15	3.69 (1.16)	3.86 (2.15)	-0.17 (1.69)	Signed Rank	1.0000
Median (min;max)	15	3.75 (2.02;5.5)	3.44 (1.44;9.13)	0.11 (-4.04;3.16)		
Q1, Q3 (IQR)	15	2.67 4.54 (1.87)	2.34 4.28 (1.94)	-0.55 0.82 (1.37)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	0.8668
Mean (Std)	30	5.43 (1.61)	5.51 (2.81)	-0.08 (1.96)	Signed Rank	0.8900
Median (min;max)	30	5.55 (3.04;8.56)	4.74 (2;11.8)	0.24 (-4.17;3.44)		
Q1, Q3 (IQR)	30	4.24 6.34 (2.1)	3.65 6.9 (3.25)	-0.79 1.18 (1.97)		

Statistics	Time point in minutes	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	0.3612
Mean (Std)	60	7.42 (2.7)	7.77 (2.81)	-0.35 (1.56)	Signed Rank	0.6195
Median (min;max)	60	6.5 (3.3;13.8)	7.48 (2.17;12.1)	-0.1 (-3.19;2.65)		
Q1, Q3 (IQR)	60	5.92 9.14 (3.22)	6.02 9.76 (3.74)	-1.1 0.27 (1.37)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	0.3841
Mean (Std)	90	6.42 (2.47)	6.73 (2.43)	-0.3 (1.4)	Signed Rank	0.7561
Median (min;max)	90	5.97 (2.35;11.8)	6.4 (1.81;11.4)	0.2 (-3.25;1.8)		
Q1, Q3 (IQR)	90	5.04 7.2 (2.16)	5.37 8.15 (2.78)	-1.41 0.54 (1.95)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	0.2670
Mean (Std)	120	5.33 (2.18)	5.65 (2.3)	-0.32 (1.16)	Signed Rank	0.4375
Median (min;max)	120	4.85 (2.08;10.7)	5.32 (1.46;11)	-0.06 (-3.23;1.17)		
Q1, Q3 (IQR)	120	4.13 5.97 (1.84)	4.23 6.37 (2.14)	-0.91 0.62 (1.53)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	0.8445
Mean (Std)	240	2.84 (1.56)	2.88 (1.62)	-0.03 (0.69)	Signed Rank	0.8176
Median (min;max)	240	2.58 (1.15;8.01)	2.39 (0.69;7.34)	0.04 (-1.9;0.9)		
Q1, Q3 (IQR)	240	1.77 3.13 (1.36)	1.96 3.23 (1.27)	-0.32 0.4 (0.72)		
n (nmiss)	360	17 (0)	16 (1)	16 (1)	Student's t	0.3500
Mean (Std)	360	1.8 (1.04)	1.99 (1.35)	-0.12 (0.49)	Signed Rank	0.8209
Median (min;max)	360	1.51 (0.8;5.14)	1.45 (0.77;6.08)	0.03 (-1.29;0.4)		
Q1, Q3 (IQR)	360	1.1 2.28 (1.18)	1.19 2.41 (1.22)	-0.33 0.24 (0.57)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-44 Difference in concentration (ng/mL): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg

Statistics	Time point in minutes	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	0	17 (0)	14 (3)	14 (3)	Student's t	0.7056
Mean (Std)	0	1.11 (0.56)	1.28 (0.76)	-0.07 (0.64)	Signed Rank	0.8926
Median (min;max)	0	1.12 (0.54;2.71)	1.13 (0.59;3.27)	-0.02 (-1.58;0.71)		
Q1, Q3 (IQR)	0	0.65 1.35 (0.7)	0.74 1.35 (0.61)	-0.51 0.49 (1)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.0246
Mean (Std)	5	1.74 (0.73)	2.33 (0.81)	-0.58 (0.97)	Signed Rank	0.0267
Median (min;max)	5	1.66 (0.8;3.41)	2.39 (1.01;3.94)	-0.88 (-1.91;1.76)		
Q1, Q3 (IQR)	5	1.16 1.99 (0.83)	1.67 2.94 (1.27)	-1.18 0.06 (1.24)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	10	2.81 (0.91)	5.47 (1.87)	-2.66 (1.94)	Signed Rank	0.0002
Median (min;max)	10	2.73 (1.37;4.72)	5.48 (2.44;8.75)	-2.65 (-5.4;1.37)		
Q1, Q3 (IQR)	10	2.42 3.24 (0.82)	3.97 6.72 (2.75)	-4.14 -1.17 (2.97)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	15	3.69 (1.16)	7.07 (2.12)	-3.38 (1.98)	Signed Rank	<.0001
Median (min;max)	15	3.75 (2.02;5.5)	6.72 (3.8;11.6)	-3.61 (-6.97;-0.76)		
Q1, Q3 (IQR)	15	2.67 4.54 (1.87)	5.69 8.81 (3.12)	-4.89 -1.35 (3.54)		

Statistics	Time point in minutes	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	30	5.43 (1.61)	10.11 (3.14)	-4.68 (2.88)	Signed Rank	<.0001
Median (min;max)	30	5.55 (3.04;8.56)	9.64 (4.84;18.5)	-4.09 (-12.39;-0.16)		
Q1, Q3 (IQR)	30	4.24 6.34 (2.1)	8.33 11.1 (2.77)	-6.1 -2.85 (3.25)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	60	7.42 (2.7)	15.36 (5.19)	-7.95 (3.54)	Signed Rank	<.0001
Median (min;max)	60	6.5 (3.3;13.8)	15 (6.02;27.8)	-7.46 (-14;-0.21)		
Q1, Q3 (IQR)	60	5.92 9.14 (3.22)	12.5 17.5 (5)	-10.33 -6.12 (4.21)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	90	6.42 (2.47)	12.95 (4.32)	-6.53 (2.86)	Signed Rank	<.0001
Median (min;max)	90	5.97 (2.35;11.8)	13.4 (4.77;19.9)	-6.79 (-11.1;-0.56)		
Q1, Q3 (IQR)	90	5.04 7.2 (2.16)	10.7 16.1 (5.4)	-8.65 -4.78 (3.87)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	120	5.33 (2.18)	10.9 (4.08)	-5.57 (2.71)	Signed Rank	<.0001
Median (min;max)	120	4.85 (2.08;10.7)	11.2 (3.81;18)	-6.15 (-10.73;-0.42)		
Q1, Q3 (IQR)	120	4.13 5.97 (1.84)	8.28 13.1 (4.82)	-7.51 -4.02 (3.49)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	240	2.84 (1.56)	5.52 (2.76)	-2.68 (1.73)	Signed Rank	<.0001
Median (min;max)	240	2.58 (1.15;8.01)	5.13 (1.53;12.6)	-2.42 (-6.15;-0.1)		
Q1, Q3 (IQR)	240	1.77 3.13 (1.36)	3.99 6.35 (2.36)	-4.16 -1.41 (2.75)		
n (nmiss)	360	17 (0)	17 (0)	17 (0)	Student's t	0.0002
Mean (Std)	360	1.8 (1.04)	3.24 (1.94)	-1.44 (1.23)	Signed Rank	0.0001
Median (min;max)	360	1.51 (0.8;5.14)	3.02 (0.94;8.55)	-1.33 (-3.93;0.22)		
Q1, Q3 (IQR)	360	1.1 2.28 (1.18)	2.25 3.31 (1.06)	-1.92 -0.33 (1.59)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-45 Difference in concentration (ng/mL): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	Time point in minutes	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	0	17 (0)	15 (2)	15 (2)	Student's t	0.2481
Mean (Std)	0	1.11 (0.56)	1.34 (0.77)	-0.17 (0.54)	Signed Rank	0.4212
Median (min;max)	0	1.12 (0.54;2.71)	1 (0.51;3.26)	-0.05 (-1.57;0.63)		
Q1, Q3 (IQR)	0	0.65 1.35 (0.7)	0.88 1.77 (0.89)	-0.32 0.12 (0.44)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.0036
Mean (Std)	5	1.74 (0.73)	2.72 (1.2)	-0.98 (1.18)	Signed Rank	0.0067
Median (min;max)	5	1.66 (0.8;3.41)	2.69 (0.86;5.72)	-0.91 (-3.11;0.75)		
Q1, Q3 (IQR)	5	1.16 1.99 (0.83)	1.71 3.49 (1.78)	-1.77 -0.06 (1.71)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.0002
Mean (Std)	10	2.81 (0.91)	4.8 (1.69)	-1.99 (1.68)	Signed Rank	0.0004
Median (min;max)	10	2.73 (1.37;4.72)	4.62 (1.76;7.07)	-2.02 (-4.53;0.89)		
Q1, Q3 (IQR)	10	2.42 3.24 (0.82)	3.56 6.12 (2.56)	-3.19 -1.08 (2.11)		

Statistics	Time point in minutes	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	15	3.69 (1.16)	6.48 (2.35)	-2.79 (2.16)	Signed Rank	0.0004
Median (min;max)	15	3.75 (2.02;5.5)	6.84 (2.55;10.2)	-3.42 (-6.84;1.49)		
Q1, Q3 (IQR)	15	2.67 4.54 (1.87)	4.91 8.29 (3.38)	-4.16 -1.97 (2.19)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	30	5.43 (1.61)	8.9 (3.05)	-3.48 (2.44)	Signed Rank	<.0001
Median (min;max)	30	5.55 (3.04;8.56)	8.09 (4.37;15.9)	-3.47 (-9;0.17)		
Q1, Q3 (IQR)	30	4.24 6.34 (2.1)	7.64 10.5 (2.86)	-4.6 -1.52 (3.08)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	60	7.42 (2.7)	13.43 (4.48)	-6.02 (3.27)	Signed Rank	<.0001
Median (min;max)	60	6.5 (3.3;13.8)	12.8 (7.21;24)	-5.19 (-14.86;-1.4)		
Q1, Q3 (IQR)	60	5.92 9.14 (3.22)	10.9 13.8 (2.9)	-6.9 -3.75 (3.15)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	90	6.42 (2.47)	12.18 (4.22)	-5.75 (2.65)	Signed Rank	<.0001
Median (min;max)	90	5.97 (2.35;11.8)	12.1 (5.16;21)	-5.25 (-10.78;-1.2)		
Q1, Q3 (IQR)	90	5.04 7.2 (2.16)	9.44 14 (4.56)	-7.51 -3.53 (3.98)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	120	5.33 (2.18)	10.27 (3.98)	-4.95 (2.34)	Signed Rank	<.0001
Median (min;max)	120	4.85 (2.08;10.7)	9.83 (3.75;19.9)	-4.81 (-9.2;-0.89)		
Q1, Q3 (IQR)	120	4.13 5.97 (1.84)	8.05 10.9 (2.85)	-6.99 -3.53 (3.46)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	240	2.84 (1.56)	5.18 (2.78)	-2.34 (1.4)	Signed Rank	<.0001
Median (min;max)	240	2.58 (1.15;8.01)	4.62 (1.58;14.1)	-2.39 (-6.09;-0.31)		
Q1, Q3 (IQR)	240	1.77 3.13 (1.36)	3.94 5.88 (1.94)	-2.85 -1.71 (1.14)		
n (nmiss)	360	17 (0)	17 (0)	17 (0)	Student's t	0.0002
Mean (Std)	360	1.8 (1.04)	3.31 (2.19)	-1.5 (1.27)	Signed Rank	<.0001
Median (min;max)	360	1.51 (0.8;5.14)	2.99 (1.01;10.7)	-1.25 (-5.56;0.07)		
Q1, Q3 (IQR)	360	1.1 2.28 (1.18)	2.17 3.84 (1.67)	-1.91 -0.84 (1.07)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-46 Difference in concentration (ng/mL): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg

Statistics	Time point in minutes	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	0	13 (4)	14 (3)	13 (4)	Student's t	0.1235
Mean (Std)	0	1.68 (1.35)	1.28 (0.76)	0.35 (0.77)	Signed Rank	0.0942
Median (min;max)	0	1.17 (0.57;5.41)	1.13 (0.59;3.27)	0.15 (-0.66;2.14)		
Q1, Q3 (IQR)	0	0.73 2.15 (1.42)	0.74 1.35 (0.61)	0.05 0.56 (0.51)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.1648
Mean (Std)	5	1.93 (1.22)	2.33 (0.81)	-0.4 (1.13)	Signed Rank	0.2069
Median (min;max)	5	1.8 (0.63;5.48)	2.39 (1.01;3.94)	-0.52 (-2.09;1.6)		
Q1, Q3 (IQR)	5	0.91 2.51 (1.6)	1.67 2.94 (1.27)	-1.14 0.26 (1.4)		

Statistics	Time point in minutes	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.0022
Mean (Std)	10	3.18 (1.82)	5.47 (1.87)	-2.29 (2.6)	Signed Rank	0.0038
Median (min;max)	10	2.69 (1.19;7.96)	5.48 (2.44;8.75)	-1.95 (-6.59;1.71)		
Q1, Q3 (IQR)	10	1.67 3.73 (2.06)	3.97 6.72 (2.75)	-4.33 -0.34 (3.99)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.0002
Mean (Std)	15	3.86 (2.15)	7.07 (2.12)	-3.21 (2.74)	Signed Rank	0.0007
Median (min;max)	15	3.44 (1.44;9.13)	6.72 (3.8;11.6)	-3.92 (-8.16;1.36)		
Q1, Q3 (IQR)	15	2.34 4.28 (1.94)	5.69 8.81 (3.12)	-4.86 -1 (3.86)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	30	5.51 (2.81)	10.11 (3.14)	-4.6 (3.36)	Signed Rank	0.0003
Median (min;max)	30	4.74 (2;11.8)	9.64 (4.84;18.5)	-4.66 (-11.6;0.7)		
Q1, Q3 (IQR)	30	3.65 6.9 (3.25)	8.33 11.1 (2.77)	-7.06 -3.25 (3.81)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	60	7.77 (2.81)	15.36 (5.19)	-7.59 (3.65)	Signed Rank	<.0001
Median (min;max)	60	7.48 (2.17;12.1)	15 (6.02;27.8)	-7.4 (-15.7;-0.48)		
Q1, Q3 (IQR)	60	6.02 9.76 (3.74)	12.5 17.5 (5)	-8.98 -5.02 (3.96)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	90	6.73 (2.43)	12.95 (4.32)	-6.22 (2.74)	Signed Rank	<.0001
Median (min;max)	90	6.4 (1.81;11.4)	13.4 (4.77;19.9)	-5.63 (-9.9;-0.23)		
Q1, Q3 (IQR)	90	5.37 8.15 (2.78)	10.7 16.1 (5.4)	-8.51 -5.07 (3.44)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	120	5.65 (2.3)	10.9 (4.08)	-5.25 (2.57)	Signed Rank	<.0001
Median (min;max)	120	5.32 (1.46;11)	11.2 (3.81;18)	-5.47 (-9.82;-0.48)		
Q1, Q3 (IQR)	120	4.23 6.37 (2.14)	8.28 13.1 (4.82)	-6.77 -3.96 (2.81)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	240	2.88 (1.62)	5.52 (2.76)	-2.64 (1.54)	Signed Rank	<.0001
Median (min;max)	240	2.39 (0.69;7.34)	5.13 (1.53;12.6)	-2.56 (-5.26;-0.49)		
Q1, Q3 (IQR)	240	1.96 3.23 (1.27)	3.99 6.35 (2.36)	-3.1 -1.52 (1.58)		
n (nmiss)	360	16 (1)	17 (0)	16 (1)	Student's t	<.0001
Mean (Std)	360	1.99 (1.35)	3.24 (1.94)	-1.4 (1.01)	Signed Rank	<.0001
Median (min;max)	360	1.45 (0.77;6.08)	3.02 (0.94;8.55)	-1.28 (-3.37;-0.03)		
Q1, Q3 (IQR)	360	1.19 2.41 (1.22)	2.25 3.31 (1.06)	-1.89 -0.66 (1.23)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-47 Difference in concentration (ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	Time point in minutes	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	0	13 (4)	15 (2)	13 (4)	Student's t	0.3423
Mean (Std)	0	1.68 (1.35)	1.34 (0.77)	0.25 (0.91)	Signed Rank	0.5417
Median (min;max)	0	1.17 (0.57;5.41)	1 (0.51;3.26)	0.06 (-0.84;2.15)		
Q1, Q3 (IQR)	0	0.73 2.15 (1.42)	0.88 1.77 (0.89)	-0.45 0.84 (1.29)		

Statistics	Time point in minutes	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.0397
Mean (Std)	5	1.93 (1.22)	2.72 (1.2)	-0.79 (1.46)	Signed Rank	0.0461
Median (min;max)	5	1.8 (0.63;5.48)	2.69 (0.86;5.72)	-0.68 (-3.79;1.87)		
Q1, Q3 (IQR)	5	0.91 2.51 (1.6)	1.71 3.49 (1.78)	-1.84 -0.29 (1.55)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.0052
Mean (Std)	10	3.18 (1.82)	4.8 (1.69)	-1.62 (2.07)	Signed Rank	0.0069
Median (min;max)	10	2.69 (1.19;7.96)	4.62 (1.76;7.07)	-1.88 (-5.08;2.4)		
Q1, Q3 (IQR)	10	1.67 3.73 (2.06)	3.56 6.12 (2.56)	-2.95 0.15 (3.1)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.0002
Mean (Std)	15	3.86 (2.15)	6.48 (2.35)	-2.62 (2.21)	Signed Rank	0.0002
Median (min;max)	15	3.44 (1.44;9.13)	6.84 (2.55;10.2)	-2.74 (-7.44;1.47)		
Q1, Q3 (IQR)	15	2.34 4.28 (1.94)	4.91 8.29 (3.38)	-3.49 -0.71 (2.78)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	0.0009
Mean (Std)	30	5.51 (2.81)	8.9 (3.05)	-3.4 (3.42)	Signed Rank	0.0007
Median (min;max)	30	4.74 (2;11.8)	8.09 (4.37;15.9)	-3.28 (-10.74;2.91)		
Q1, Q3 (IQR)	30	3.65 6.9 (3.25)	7.64 10.5 (2.86)	-4.69 -1.49 (3.2)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	60	7.77 (2.81)	13.43 (4.48)	-5.66 (4.08)	Signed Rank	<.0001
Median (min;max)	60	7.48 (2.17;12.1)	12.8 (7.21;24)	-5.16 (-17.51;-0.5)		
Q1, Q3 (IQR)	60	6.02 9.76 (3.74)	10.9 13.8 (2.9)	-6.84 -3.42 (3.42)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	90	6.73 (2.43)	12.18 (4.22)	-5.45 (2.72)	Signed Rank	<.0001
Median (min;max)	90	6.4 (1.81;11.4)	12.1 (5.16;21)	-4.85 (-10.4;-0.87)		
Q1, Q3 (IQR)	90	5.37 8.15 (2.78)	9.44 14 (4.56)	-8.11 -3.75 (4.36)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	120	5.65 (2.3)	10.27 (3.98)	-4.62 (2.29)	Signed Rank	<.0001
Median (min;max)	120	5.32 (1.46;11)	9.83 (3.75;19.9)	-4.37 (-8.9;-0.95)		
Q1, Q3 (IQR)	120	4.23 6.37 (2.14)	8.05 10.9 (2.85)	-6.22 -3.12 (3.1)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	240	2.88 (1.62)	5.18 (2.78)	-2.3 (1.44)	Signed Rank	<.0001
Median (min;max)	240	2.39 (0.69;7.34)	4.62 (1.58;14.1)	-2.14 (-6.76;-0.62)		
Q1, Q3 (IQR)	240	1.96 3.23 (1.27)	3.94 5.88 (1.94)	-2.54 -1.76 (0.78)		
n (nmiss)	360	16 (1)	17 (0)	16 (1)	Student's t	<.0001
Mean (Std)	360	1.99 (1.35)	3.31 (2.19)	-1.46 (1)	Signed Rank	<.0001
Median (min;max)	360	1.45 (0.77;6.08)	2.99 (1.01;10.7)	-1.36 (-4.62;-0.24)		
Q1, Q3 (IQR)	360	1.19 2.41 (1.22)	2.17 3.84 (1.67)	-1.56 -0.91 (0.65)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-48 Difference in concentration (ng/mL): ZYN[®] Smooth 6 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	Time point in minutes	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	0	14 (3)	15 (2)	14 (3)	Student's t	0.5076
Mean (Std)	0	1.28 (0.76)	1.34 (0.77)	-0.11 (0.59)	Signed Rank	0.2676
Median (min;max)	0	1.13 (0.59;3.27)	1 (0.51;3.26)	-0.18 (-0.83;1.44)		
Q1, Q3 (IQR)	0	0.74 1.35 (0.61)	0.88 1.77 (0.89)	-0.56 0.12 (0.68)		
n (nmiss)	5	17 (0)	17 (0)	17 (0)	Student's t	0.2043
Mean (Std)	5	2.33 (0.81)	2.72 (1.2)	-0.39 (1.23)	Signed Rank	0.1901
Median (min;max)	5	2.39 (1.01;3.94)	2.69 (0.86;5.72)	-0.55 (-2.65;2.08)		
Q1, Q3 (IQR)	5	1.67 2.94 (1.27)	1.71 3.49 (1.78)	-1.29 0.33 (1.62)		
n (nmiss)	10	17 (0)	17 (0)	17 (0)	Student's t	0.1309
Mean (Std)	10	5.47 (1.87)	4.8 (1.69)	0.67 (1.73)	Signed Rank	0.2069
Median (min;max)	10	5.48 (2.44;8.75)	4.62 (1.76;7.07)	0.71 (-2.13;4.68)		
Q1, Q3 (IQR)	10	3.97 6.72 (2.75)	3.56 6.12 (2.56)	-0.48 1.51 (1.99)		
n (nmiss)	15	17 (0)	17 (0)	17 (0)	Student's t	0.2435
Mean (Std)	15	7.07 (2.12)	6.48 (2.35)	0.59 (2.01)	Signed Rank	0.1901
Median (min;max)	15	6.72 (3.8;11.6)	6.84 (2.55;10.2)	0.72 (-3.47;4.51)		
Q1, Q3 (IQR)	15	5.69 8.81 (3.12)	4.91 8.29 (3.38)	-0.29 1.35 (1.64)		
n (nmiss)	30	17 (0)	17 (0)	17 (0)	Student's t	0.0714
Mean (Std)	30	10.11 (3.14)	8.9 (3.05)	1.2 (2.57)	Signed Rank	0.0714
Median (min;max)	30	9.64 (4.84;18.5)	8.09 (4.37;15.9)	1.14 (-2.9;7.1)		
Q1, Q3 (IQR)	30	8.33 11.1 (2.77)	7.64 10.5 (2.86)	-0.3 2.57 (2.87)		
n (nmiss)	60	17 (0)	17 (0)	17 (0)	Student's t	0.0254
Mean (Std)	60	15.36 (5.19)	13.43 (4.48)	1.93 (3.23)	Signed Rank	0.0105
Median (min;max)	60	15 (6.02;27.8)	12.8 (7.21;24)	2.5 (-7.4;6.1)		
Q1, Q3 (IQR)	60	12.5 17.5 (5)	10.9 13.8 (2.9)	0.3 3.8 (3.5)		
n (nmiss)	90	17 (0)	17 (0)	17 (0)	Student's t	0.1929
Mean (Std)	90	12.95 (4.32)	12.18 (4.22)	0.77 (2.35)	Signed Rank	0.2200
Median (min;max)	90	13.4 (4.77;19.9)	12.1 (5.16;21)	0.6 (-3.15;4.76)		
Q1, Q3 (IQR)	90	10.7 16.1 (5.4)	9.44 14 (4.56)	-0.6 2.2 (2.8)		
n (nmiss)	120	17 (0)	17 (0)	17 (0)	Student's t	0.2015
Mean (Std)	120	10.9 (4.08)	10.27 (3.98)	0.63 (1.94)	Signed Rank	0.2069
Median (min;max)	120	11.2 (3.81;18)	9.83 (3.75;19.9)	0.8 (-2.3;3.65)		
Q1, Q3 (IQR)	120	8.28 13.1 (4.82)	8.05 10.9 (2.85)	-0.47 1.88 (2.35)		
n (nmiss)	240	17 (0)	17 (0)	17 (0)	Student's t	0.3245
Mean (Std)	240	5.52 (2.76)	5.18 (2.78)	0.34 (1.39)	Signed Rank	0.4104
Median (min;max)	240	5.13 (1.53;12.6)	4.62 (1.58;14.1)	0.05 (-1.57;2.74)		
Q1, Q3 (IQR)	240	3.99 6.35 (2.36)	3.94 5.88 (1.94)	-0.77 1.48 (2.25)		
n (nmiss)	360	17 (0)	17 (0)	17 (0)	Student's t	0.7758
Mean (Std)	360	3.24 (1.94)	3.31 (2.19)	-0.07 (0.94)	Signed Rank	0.8900
Median (min;max)	360	3.02 (0.94;8.55)	2.99 (1.01;10.7)	-0.15 (-2.15;1.77)		
Q1, Q3 (IQR)	360	2.25 3.31 (1.06)	2.17 3.84 (1.67)	-0.66 0.32 (0.98)		

SM17_03 Analysis of secondary endpoint - concentration, SAS program:
sec_endpoint_concentration.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:06:18

Table 14.3-49 Nicotine concentration (ng/mL) by treatment

Name of Actual Treatment	Planned Time Point Name	Analyte (unit)	N	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN® Smooth 3 mg	Timepoint 0:00	Nicotine (ng/mL)	17	0.54	1.12	2.71	1.11	50.5	0.994
	Timepoint 0:05	Nicotine (ng/mL)	17	0.8	1.66	3.41	1.74	41.7	1.61
	Timepoint 0:10	Nicotine (ng/mL)	17	1.37	2.73	4.72	2.81	32.3	2.67
	Timepoint 0:15	Nicotine (ng/mL)	17	2.02	3.75	5.5	3.69	31.4	3.5
	Timepoint 0:30	Nicotine (ng/mL)	17	3.04	5.55	8.56	5.43	29.6	5.2
	Timepoint 1:00	Nicotine (ng/mL)	17	3.3	6.5	13.8	7.42	36.3	6.96
	Timepoint 1:30	Nicotine (ng/mL)	17	2.35	5.97	11.8	6.42	38.5	5.99
	Timepoint 2:00	Nicotine (ng/mL)	17	2.08	4.85	10.7	5.33	40.8	4.95
	Timepoint 4:00	Nicotine (ng/mL)	17	1.15	2.58	8.01	2.84	54.9	2.56
	Timepoint 6:00	Nicotine (ng/mL)	17	0.801	1.51	5.14	1.8	57.8	1.6
ZYN® Smooth 6 mg	Timepoint 0:00	Nicotine (ng/mL)	14	0.593	1.13	3.27	1.28	59.5	1.12
	Timepoint 0:05	Nicotine (ng/mL)	17	1.01	2.39	3.94	2.33	34.7	2.18
	Timepoint 0:10	Nicotine (ng/mL)	17	2.44	5.48	8.75	5.47	34.2	5.15
	Timepoint 0:15	Nicotine (ng/mL)	17	3.8	6.72	11.6	7.07	30	6.78
	Timepoint 0:30	Nicotine (ng/mL)	17	4.84	9.64	18.5	10.1	31	9.68
	Timepoint 1:00	Nicotine (ng/mL)	17	6.02	15	27.8	15.4	33.8	14.5
	Timepoint 1:30	Nicotine (ng/mL)	17	4.77	13.4	19.9	13	33.3	12.1
	Timepoint 2:00	Nicotine (ng/mL)	17	3.81	11.2	18	10.9	37.4	10.1
	Timepoint 4:00	Nicotine (ng/mL)	17	1.53	5.13	12.6	5.52	50.1	4.89
	Timepoint 6:00	Nicotine (ng/mL)	17	0.94	3.02	8.55	3.24	59.7	2.76
ZYN® Smooth 3 mg (alt. manu. proc.)	Timepoint 0:00	Nicotine (ng/mL)	13	0.574	1.17	5.41	1.68	79.9	1.34
	Timepoint 0:05	Nicotine (ng/mL)	17	0.634	1.8	5.48	1.93	63.2	1.63
	Timepoint 0:10	Nicotine (ng/mL)	17	1.19	2.69	7.96	3.18	57.1	2.75
	Timepoint 0:15	Nicotine (ng/mL)	17	1.44	3.44	9.13	3.86	55.6	3.4
	Timepoint 0:30	Nicotine (ng/mL)	17	2	4.74	11.8	5.51	51.1	4.9
	Timepoint 1:00	Nicotine (ng/mL)	17	2.17	7.48	12.1	7.77	36.1	7.21
	Timepoint 1:30	Nicotine (ng/mL)	17	1.81	6.4	11.4	6.73	36.2	6.25
	Timepoint 2:00	Nicotine (ng/mL)	17	1.46	5.32	11	5.65	40.7	5.18
	Timepoint 4:00	Nicotine (ng/mL)	17	0.689	2.39	7.34	2.88	56.3	2.51
	Timepoint 6:00	Nicotine (ng/mL)	16	0.766	1.45	6.08	1.99	68.1	1.69
ZYN® Smooth 6 mg (alt. manu. proc.)	Timepoint 0:00	Nicotine (ng/mL)	15	0.512	0.999	3.26	1.34	57.5	1.18
	Timepoint 0:05	Nicotine (ng/mL)	17	0.861	2.69	5.72	2.72	44.2	2.45
	Timepoint 0:10	Nicotine (ng/mL)	17	1.76	4.62	7.07	4.8	35.2	4.48
	Timepoint 0:15	Nicotine (ng/mL)	17	2.55	6.84	10.2	6.48	36.3	6.01
	Timepoint 0:30	Nicotine (ng/mL)	17	4.37	8.09	15.9	8.9	34.3	8.41
	Timepoint 1:00	Nicotine (ng/mL)	17	7.21	12.8	24	13.4	33.4	12.8
	Timepoint 1:30	Nicotine (ng/mL)	17	5.16	12.1	21	12.2	34.6	11.5
	Timepoint 2:00	Nicotine (ng/mL)	17	3.75	9.83	19.9	10.3	38.8	9.54
	Timepoint 4:00	Nicotine (ng/mL)	17	1.58	4.62	14.1	5.18	53.8	4.6
	Timepoint 6:00	Nicotine (ng/mL)	17	1.01	2.99	10.7	3.31	66.3	2.83
Swedish portion snus PSWL 1 0 g (8 mg)	Timepoint 0 00	Nicotine (ng/mL)	13	0 593	1 05	3 06	1 33	50 1	1 2
	Timepoint 0:05	Nicotine (ng/mL)	17	0.504	1.94	5.48	2.36	59.9	1.98

Name of Actual Treatment	Planned Time Point Name	Analyte (unit)	N	Min	Median	Max	Mean	CV (%)	Geometric Mean
	Timepoint 0:10	Nicotine (ng/mL)	17	0.738	3.75	7.38	4.09	42.7	3.65
	Timepoint 0:15	Nicotine (ng/mL)	17	1.19	4.87	9.09	4.94	39.1	4.53
	Timepoint 0:30	Nicotine (ng/mL)	17	2.52	6.63	12.8	7.19	36	6.74
	Timepoint 1:00	Nicotine (ng/mL)	17	4.79	9.41	17.5	10.2	29.7	9.75
	Timepoint 1:30	Nicotine (ng/mL)	17	5.45	9.48	19.5	9.63	36.9	9.11
	Timepoint 2:00	Nicotine (ng/mL)	17	4.21	8.23	19.3	8.21	43	7.65
	Timepoint 4:00	Nicotine (ng/mL)	17	1.8	3.29	14.1	4.18	66.3	3.7
	Timepoint 6:00	Nicotine (ng/mL)	17	1.29	2.03	10.8	2.68	83	2.26

Values <0.500 ng/mL (BLQ) handled as missing in summary tables

SM17_03 PK conc data, SAS program: pc_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-29T11:54:39

14.3.2.6 Difference in pharmacokinetic parameters (non-baseline adjusted data, N=17)

Table 14.3-50 Difference in AUC_{0-t} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0001
Mean (Std)	2114.25 (935.29)	1445.91 (560.24)	668.34 (539.86)	Signed Rank	<.0001
Median (min;max)	1941.81 (1086.26;5237.63)	1389.43 (638.84;2960.5)	613.01 (-141.98;2277.13)		
Q1, Q3 (IQR)	1584.42 2173.28 (588.86)	1098.78 1684.45 (585.67)	327.29 813.35 (486.06)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-51 Difference in AUC_{0-t} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0010
Mean (Std)	2114.25 (935.29)	1504.98 (661.12)	609.27 (625.63)	Signed Rank	0.0007
Median (min;max)	1941.81 (1086.26;5237.63)	1420.43 (341.71;2958.7)	487.8 (-555.6;2278.93)		
Q1, Q3 (IQR)	1584.42 2173.28 (588.86)	1083.1 1645.53 (562.43)	308.27 885.01 (576.74)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-52 Difference in AUC_{0-t} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0005
Mean (Std)	2114.25 (935.29)	2865.76 (1000.68)	-751.51 (709.67)	Signed Rank	0.0007
Median (min;max)	1941.81 (1086.26;5237.63)	2745.31 (1135.35;4800.38)	-821 (-1848.72;437.25)		
Q1, Q3 (IQR)	1584.42 2173.28 (588.86)	2371.15 3638.53 (1267.38)	-1249.79 -445.64 (804.15)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-53 Difference in AUC_{0-t} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0012
Mean (Std)	2114.25 (935.29)	2658.2 (990.85)	-543.95 (572.76)	Signed Rank	0.0017
Median (min;max)	1941.81 (1086.26;5237.63)	2667.93 (1145.62;5246.52)	-569.06 (-1588.97;431.12)		
Q1, Q3 (IQR)	1584.42 2173.28 (588.86)	2125.65 2952.13 (826.48)	-1003.53 -8.9 (994.63)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-54 Difference in AUC_{0-t} (min*ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.4285
Mean (Std)	1445.91 (560.24)	1504.98 (661.12)	-59.08 (299.87)	Signed Rank	0.9265
Median (min;max)	1389.43 (638.84;2960.5)	1420.43 (341.71;2958.7)	14.9 (-882.89;298.93)		
Q1, Q3 (IQR)	1098.78 1684.45 (585.67)	1083.1 1645.53 (562.43)	-172.35 113.46 (285.81)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-55 Difference in AUC_{0-t} (min*ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1445.91 (560.24)	2865.76 (1000.68)	-1419.85 (646.13)	Signed Rank	<.0001
Median (min;max)	1389.43 (638.84;2960.5)	2745.31 (1135.35;4800.38)	-1242.77 (-2461.73;-55.84)		
Q1, Q3 (IQR)	1098.78 1684.45 (585.67)	2371.15 3638.53 (1267.38)	-1841.09 -1074.64 (766.45)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-56 Difference in AUC_{0-t} (min*ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1445.91 (560.24)	2658.2 (990.85)	-1212.29 (554.3)	Signed Rank	<.0001
Median (min;max)	1389.43 (638.84;2960.5)	2667.93 (1145.62;5246.52)	-1154.69 (-2286.03;-197.54)		
Q1, Q3 (IQR)	1098.78 1684.45 (585.67)	2125.65 2952.13 (826.48)	-1709.12 -783.48 (925.64)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-57 Difference in AUC_{0-t} (min*ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1504.98 (661.12)	2865.76 (1000.68)	-1360.77 (588.06)	Signed Rank	<.0001
Median (min;max)	1420.43 (341.71;2958.7)	2745.31 (1135.35;4800.38)	-1284.02 (-2468.44;-106.7)		
Q1, Q3 (IQR)	1083.1 1645.53 (562.43)	2371.15 3638.53 (1267.38)	-1820.16 -958.2 (861.96)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-58 *Difference in AUC_{0-t} (min*ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)*

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	1504.98 (661.12)	2658.2 (990.85)	-1153.21 (576.22)	Signed Rank	<.0001
Median (min;max)	1420.43 (341.71;2958.7)	2667.93 (1145.62;5246.52)	-1022.41 (-2287.83;-248.4)		
Q1, Q3 (IQR)	1083.1 1645.53 (562.43)	2125.65 2952.13 (826.48)	-1336.62 -885.51 (451.11)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-59 *Difference in AUC_{0-t} (min*ng/mL): ZYN[®] Smooth 6 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)*

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.1121
Mean (Std)	2865.76 (1000.68)	2658.2 (990.85)	207.56 (508.97)	Signed Rank	0.1594
Median (min;max)	2745.31 (1135.35;4800.38)	2667.93 (1145.62;5246.52)	195.57 (-767.97;1056.11)		
Q1, Q3 (IQR)	2371.15 3638.53 (1267.38)	2125.65 2952.13 (826.48)	-141.7 686.4 (828.1)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-60 *Difference in AUC_{60min} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg*

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0009
Mean (Std)	396.62 (120.82)	294.71 (89.14)	101.92 (103.76)	Signed Rank	0.0013
Median (min;max)	375.63 (146.66;602.63)	281.65 (160.94;463.45)	95.97 (-77.48;317.61)		
Q1, Q3 (IQR)	305.31 501.33 (196.02)	224.14 377.32 (153.18)	43.29 160.3 (117.01)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-61 *Difference in AUC_{60min} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)*

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0228
Mean (Std)	396.62 (120.82)	307.27 (133.95)	89.35 (146.22)	Signed Rank	0.0267
Median (min;max)	375.63 (146.66;602.63)	266.18 (104.02;595.03)	112.06 (-232.38;313.59)		
Q1, Q3 (IQR)	305.31 501.33 (196.02)	222.74 373.73 (150.99)	32.28 170.9 (138.62)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-62 *Difference in AUC_{60min} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg*

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0001
Mean (Std)	396.62 (120.82)	568.89 (164.93)	-172.26 (143.97)	Signed Rank	0.0007
Median (min;max)	375.63 (146.66;602.63)	522.88 (256.8;935.1)	-177.85 (-433.78;41.33)		

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
Q1, Q3 (IQR)	305.31 501.33 (196.02)	484.8 626.95 (142.15)	-256.88 -122.94 (133.94)		
SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43					

Table 14.3-63 Difference in AUC_{60min} (min*ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0082
Mean (Std)	396.62 (120.82)	502.68 (152.81)	-106.06 (144.95)	Signed Rank	0.0110
Median (min;max)	375.63 (146.66;602.63)	458.02 (254.35;823.43)	-113.48 (-435.32;79.61)		
Q1, Q3 (IQR)	305.31 501.33 (196.02)	439.5 546.01 (106.51)	-159.68 20.23 (179.91)		
SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43					

Table 14.3-64 Difference in AUC_{60min} (min*ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.5534
Mean (Std)	294.71 (89.14)	307.27 (133.95)	-12.56 (85.55)	Signed Rank	0.7819
Median (min;max)	281.65 (160.94;463.45)	266.18 (104.02;595.03)	-4.02 (-208.3;127.46)		
Q1, Q3 (IQR)	224.14 377.32 (153.18)	222.74 373.73 (150.99)	-39.46 43.61 (83.07)		
SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43					

Table 14.3-65 Difference in AUC_{60min} (min*ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	294.71 (89.14)	568.89 (164.93)	-274.18 (132.05)	Signed Rank	<.0001
Median (min;max)	281.65 (160.94;463.45)	522.88 (256.8;935.1)	-267.1 (-567.45;-14.83)		
Q1, Q3 (IQR)	224.14 377.32 (153.18)	484.8 626.95 (142.15)	-336.71 -194.56 (142.15)		
SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43					

Table 14.3-66 Difference in AUC_{60min} (min*ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	294.71 (89.14)	502.68 (152.81)	-207.98 (124.63)	Signed Rank	<.0001
Median (min;max)	281.65 (160.94;463.45)	458.02 (254.35;823.43)	-221.91 (-523.68;-12.39)		
Q1, Q3 (IQR)	224.14 377.32 (153.18)	439.5 546.01 (106.51)	-253.33 -145.7 (107.63)		
SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43					

Table 14.3-67 Difference in AUC_{60min} (min*ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	307.27 (133.95)	568.89 (164.93)	-261.62 (162.56)	Signed Rank	<.0001
Median (min;max)	266.18 (104.02;595.03)	522.88 (256.8;935.1)	-259.44 (-570.64;4.01)		
Q1, Q3 (IQR)	222.74 373.73 (150.99)	484.8 626.95 (142.15)	-342.17 -182.13 (160.04)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-68 Difference in AUC_{60min} (min*ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0001
Mean (Std)	307.27 (133.95)	502.68 (152.81)	-195.41 (160.35)	Signed Rank	0.0002
Median (min;max)	266.18 (104.02;595.03)	458.02 (254.35;823.43)	-213.87 (-606.23;80.4)		
Q1, Q3 (IQR)	222.74 373.73 (150.99)	439.5 546.01 (106.51)	-243.42 -132.61 (110.81)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-69 Difference in AUC_{60min} (min*ng/mL): ZYN[®] Smooth 6 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0190
Mean (Std)	568.89 (164.93)	502.68 (152.81)	66.21 (104.59)	Signed Rank	0.0110
Median (min;max)	522.88 (256.8;935.1)	458.02 (254.35;823.43)	69.85 (-178.45;274.1)		
Q1, Q3 (IQR)	484.8 626.95 (142.15)	439.5 546.01 (106.51)	33.24 83.38 (50.14)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-70 Difference in C_{max} (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0001
Mean (Std)	10.57 (3.29)	7.52 (2.7)	3.04 (2.53)	Signed Rank	<.0001
Median (min;max)	9.92 (5.45;19.5)	6.92 (3.52;13.8)	2.1 (-0.7;7.9)		
Q1, Q3 (IQR)	8.51 12 (3.49)	5.92 9.14 (3.22)	1.59 4.63 (3.04)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-71 Difference in C_{max} (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0012
Mean (Std)	10.57 (3.29)	7.83 (2.86)	2.74 (2.86)	Signed Rank	0.0021
Median (min;max)	9.92 (5.45;19.5)	7.48 (2.17;12.1)	2.34 (-2.27;8.1)		
Q1, Q3 (IQR)	8.51 12 (3.49)	6.02 9.76 (3.74)	1.48 4.23 (2.75)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-72 Difference in C_{max} (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	10.57 (3.29)	15.5 (5.24)	-4.94 (3.85)	Signed Rank	0.0004
Median (min;max)	9.92 (5.45;19.5)	15 (6.02;27.8)	-5.3 (-12.4;1.29)		
Q1, Q3 (IQR)	8.51 12 (3.49)	12.5 18.1 (5.6)	-6.95 -3.8 (3.15)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-73 Difference in C_{max} (ng/mL): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0012
Mean (Std)	10.57 (3.29)	13.86 (4.64)	-3.29 (3.46)	Signed Rank	0.0004
Median (min;max)	9.92 (5.45;19.5)	12.8 (7.21;24)	-3.3 (-13.02;0.6)		
Q1, Q3 (IQR)	8.51 12 (3.49)	11.4 14.4 (3)	-4.45 -1 (3.45)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-74 Difference in C_{max} (ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.4346
Mean (Std)	7.52 (2.7)	7.83 (2.86)	-0.31 (1.57)	Signed Rank	0.6110
Median (min;max)	6.92 (3.52;13.8)	7.48 (2.17;12.1)	-0.1 (-3.19;2.65)		
Q1, Q3 (IQR)	5.92 9.14 (3.22)	6.02 9.76 (3.74)	-1.06 0.27 (1.33)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-75 Difference in C_{max} (ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	7.52 (2.7)	15.5 (5.24)	-7.98 (3.6)	Signed Rank	<.0001
Median (min;max)	6.92 (3.52;13.8)	15 (6.02;27.8)	-7.8 (-14;-0.21)		
Q1, Q3 (IQR)	5.92 9.14 (3.22)	12.5 18.1 (5.6)	-10.33 -5.58 (4.75)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-76 Difference in C_{max} (ng/mL): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	7.52 (2.7)	13.86 (4.64)	-6.34 (3.3)	Signed Rank	<.0001
Median (min;max)	6.92 (3.52;13.8)	12.8 (7.21;24)	-5.79 (-14.86;-1.4)		
Q1, Q3 (IQR)	5.92 9.14 (3.22)	11.4 14.4 (3)	-6.93 -3.9 (3.03)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-77 Difference in C_{max} (ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	7.83 (2.86)	15.5 (5.24)	-7.68 (3.63)	Signed Rank	<.0001
Median (min;max)	7.48 (2.17;12.1)	15 (6.02;27.8)	-7.96 (-15.7;-0.48)		
Q1, Q3 (IQR)	6.02 9.76 (3.74)	12.5 18.1 (5.6)	-8.98 -5.02 (3.96)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-78 Difference in C_{max} (ng/mL): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	<.0001
Mean (Std)	7.83 (2.86)	13.86 (4.64)	-6.03 (4.04)	Signed Rank	<.0001
Median (min;max)	7.48 (2.17;12.1)	12.8 (7.21;24)	-5.16 (-17.51;-1)		
Q1, Q3 (IQR)	6.02 9.76 (3.74)	11.4 14.4 (3)	-6.84 -3.63 (3.21)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-79 *Difference in C_{max} (ng/mL): ZYN[®] Smooth 6 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)*

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0580
Mean (Std)	15.5 (5.24)	13.86 (4.64)	1.65 (3.32)	Signed Rank	0.0493
Median (min;max)	15 (6.02;27.8)	12.8 (7.21;24)	2.5 (-7.4;6.1)		
Q1, Q3 (IQR)	12.5 18.1 (5.6)	11.4 14.4 (3)	0.3 3.8 (3.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-80 *Difference in terminal half-life (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg*

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.3718
Mean (Std)	143.58 (47.31)	158.57 (67.52)	-14.99 (67.27)	Signed Rank	0.5477
Median (min;max)	129.12 (98.36;286.54)	150.5 (96.27;388.01)	-1.79 (-248.07;59.65)		
Q1, Q3 (IQR)	110.66 157 (46.34)	116.06 168.77 (52.71)	-14.7 4.46 (19.16)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-81 *Difference in terminal half-life (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)*

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.8814
Mean (Std)	143.58 (47.31)	143.09 (46.74)	0.49 (13.27)	Signed Rank	0.5791
Median (min;max)	129.12 (98.36;286.54)	131.25 (89.78;278.5)	2.26 (-36.79;22.31)		
Q1, Q3 (IQR)	110.66 157 (46.34)	114.27 170.6 (56.33)	-3.69 8.57 (12.26)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-82 *Difference in terminal half-life (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg*

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.2537
Mean (Std)	143.58 (47.31)	135.76 (37.24)	7.82 (27.23)	Signed Rank	0.1594
Median (min;max)	129.12 (98.36;286.54)	129.38 (70.71;223.46)	7.31 (-58.48;63.08)		
Q1, Q3 (IQR)	110.66 157 (46.34)	107.73 158.63 (50.9)	-0.26 25.96 (26.22)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-83 *Difference in terminal half-life (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg (alt. manu. proc.)*

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.9923
Mean (Std)	143.58 (47.31)	143.63 (42.79)	-0.05 (21.93)	Signed Rank	0.7819
Median (min;max)	129.12 (98.36;286.54)	137.2 (83.72;268.11)	-3.32 (-33.61;51.29)		
Q1, Q3 (IQR)	110.66 157 (46.34)	120.41 163.21 (42.8)	-21.09 15.63 (36.72)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-84 *Difference in terminal half-life (min): ZYN® Smooth 3 mg vs. ZYN® Smooth 3 mg (alt. manu. proc.)*

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.2864
Mean (Std)	158.57 (67.52)	143.09 (46.74)	15.48 (57.88)	Signed Rank	0.4038
Median (min;max)	150.5 (96.27;388.01)	131.25 (89.78;278.5)	3.12 (-51.61;211.28)		
Q1, Q3 (IQR)	116.06 168.77 (52.71)	114.27 170.6 (56.33)	-6.7 19.71 (26.41)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-85 *Difference in terminal half-life (min): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg*

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.1310
Mean (Std)	158.57 (67.52)	135.76 (37.24)	22.81 (59.09)	Signed Rank	0.0638
Median (min;max)	150.5 (96.27;388.01)	129.38 (70.71;223.46)	10.88 (-45.35;229.3)		
Q1, Q3 (IQR)	116.06 168.77 (52.71)	107.73 158.63 (50.9)	-2.15 25.56 (27.71)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-86 *Difference in terminal half-life (min): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)*

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.3137
Mean (Std)	158.57 (67.52)	143.63 (42.79)	14.94 (59.22)	Signed Rank	0.6112
Median (min;max)	150.5 (96.27;388.01)	137.2 (83.72;268.11)	4.39 (-41.22;224.03)		
Q1, Q3 (IQR)	116.06 168.77 (52.71)	120.41 163.21 (42.8)	-20.28 16.2 (36.48)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-87 Difference in terminal half-life (min): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.2017
Mean (Std)	143.09 (46.74)	135.76 (37.24)	7.33 (22.7)	Signed Rank	0.1901
Median (min;max)	131.25 (89.78;278.5)	129.38 (70.71;223.46)	1.98 (-46.65;55.04)		
Q1, Q3 (IQR)	114.27 170.6 (56.33)	107.73 158.63 (50.9)	-6.02 21.22 (27.24)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-88 Difference in terminal half-life (min): ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.9081
Mean (Std)	143.09 (46.74)	143.63 (42.79)	-0.54 (18.98)	Signed Rank	0.7467
Median (min;max)	131.25 (89.78;278.5)	137.2 (83.72;268.11)	-3.65 (-31.96;53.64)		
Q1, Q3 (IQR)	114.27 170.6 (56.33)	120.41 163.21 (42.8)	-8.78 10.39 (19.17)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-89 Difference in terminal half-life (min): ZYN® Smooth 6 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.1093
Mean (Std)	135.76 (37.24)	143.63 (42.79)	-7.87 (19.14)	Signed Rank	0.1202
Median (min;max)	129.38 (70.71;223.46)	137.2 (83.72;268.11)	-7.96 (-44.65;24.87)		
Q1, Q3 (IQR)	107.73 158.63 (50.9)	120.41 163.21 (42.8)	-15.74 4.04 (19.78)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-90 Difference in T_{max} (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg

Statistics	PSWL	ZS3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.3552
Mean (Std)	68.88 (17.61)	63.82 (14.5)	5.06 (21.91)	Signed Rank	0.4668
Median (min;max)	60 (30;90)	60 (30;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 90 (30)	60 62 (2)	-2 30 (32)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-91 Difference in T_{max} (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	PSWL	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0556
Mean (Std)	68.88 (17.61)	58.29 (12.87)	10.59 (21.15)	Signed Rank	0.1016
Median (min;max)	60 (30;90)	60 (30;90)	0 (-31;60)		
Q1, Q3 (IQR)	60 90 (30)	60 60 (0)	0 30 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-92 Difference in T_{max} (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg

Statistics	PSWL	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0925
Mean (Std)	68.88 (17.61)	60.88 (15.43)	8 (18.44)	Signed Rank	0.1094
Median (min;max)	60 (30;90)	60 (15;90)	0 (-30;45)		
Q1, Q3 (IQR)	60 90 (30)	60 60 (0)	0 30 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-93 Difference in T_{max} (min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	PSWL	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.6580
Mean (Std)	68.88 (17.61)	70.71 (14.82)	-1.82 (16.67)	Signed Rank	0.6875
Median (min;max)	60 (30;90)	60 (60;91)	0 (-30;30)		
Q1, Q3 (IQR)	60 90 (30)	60 90 (30)	-1 0 (1)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-94 Difference in T_{max} (min): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.2484
Mean (Std)	63.82 (14.5)	58.29 (12.87)	5.53 (19.03)	Signed Rank	0.2188
Median (min;max)	60 (30;90)	60 (30;90)	0 (-30;60)		
Q1, Q3 (IQR)	60 62 (2)	60 60 (0)	0 2 (2)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-95 Difference in T_{max} (min): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.3722
Mean (Std)	63.82 (14.5)	60.88 (15.43)	2.94 (13.21)	Signed Rank	0.3125
Median (min;max)	60 (30;90)	60 (15;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 62 (2)	60 60 (0)	0 2 (2)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-96 Difference in T_{max} (min): ZYN[®] Smooth 3 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.1162
Mean (Std)	63.82 (14.5)	70.71 (14.82)	-6.88 (17.08)	Signed Rank	0.1797
Median (min;max)	60 (30;90)	60 (60;91)	0 (-31;30)		
Q1, Q3 (IQR)	60 62 (2)	60 90 (30)	-30 0 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-97 Difference in T_{max} (min): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg

Statistics	ZSA3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.6013
Mean (Std)	58.29 (12.87)	60.88 (15.43)	-2.59 (20.02)	Signed Rank	0.8750
Median (min;max)	60 (30;90)	60 (15;90)	0 (-60;45)		
Q1, Q3 (IQR)	60 60 (0)	60 60 (0)	0 0 (0)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-98 Difference in T_{max} (min): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0147
Mean (Std)	58.29 (12.87)	70.71 (14.82)	-12.41 (18.72)	Signed Rank	0.0234
Median (min;max)	60 (30;90)	60 (60;91)	0 (-61;1)		
Q1, Q3 (IQR)	60 60 (0)	60 90 (30)	-30 0 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

Table 14.3-99 Difference in T_{max} (min): ZYN[®] Smooth 6 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	17 (0)	17 (0)	17 (0)	Student's t	0.0207
Mean (Std)	60.88 (15.43)	70.71 (14.82)	-9.82 (15.78)	Signed Rank	0.0156
Median (min;max)	60 (15;90)	60 (60;91)	0 (-45;0)		
Q1, Q3 (IQR)	60 60 (0)	60 90 (30)	-30 0 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: sec_endpoint_auc.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-04-05T07:16:43

14.3.2.7 Difference in pharmacokinetic parameters (non-baseline adjusted data, N=12)

Table 14.3-100 Pharmacokinetic parameters by treatment

Name of Actual Treatment	Analyte (unit)	N	NMiss	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN® Smooth 3 mg	AUC0-60 (min*ng/mL)	12	5	161	248.8	463	272.9	34.67	259.1
	AUC0-inf (min*ng/mL)	12	5	827	1416	2680	1501	32.33	1437
	AUC0-last (min*ng/mL)	12	5	631	1162	2290	1244	34.62	1181
	Cmax (ng/mL)	12	5	3.52	6.325	13.8	7.103	40.43	6.621
	T1/2(z) (min)	12	5	96.3	125	175	132.7	19.47	130.5
	Tmax (min)	12	5	30	60	90	60.42	21.24	58.98
ZYN® Smooth 6 mg	AUC0-60 (min*ng/mL)	12	5	257	522.8	935	559.7	34.86	529.6
	AUC0-inf (min*ng/mL)	12	5	1260	3142	4930	2987	35.51	2792
	AUC0-last (min*ng/mL)	12	5	1110	2632	3960	2541	34.19	2384
	Cmax (ng/mL)	12	5	6.02	14.5	27.8	15.04	40.21	13.89
	T1/2(z) (min)	12	5	70.7	122.6	159	118.7	21.3	116.1
	Tmax (min)	12	5	15	60	60	56.25	23.09	53.45
ZYN® Smooth 3 mg (alt. manu. proc.)	AUC0-60 (min*ng/mL)	12	5	104	234.4	417	254.7	37.9	237.8
	AUC0-inf (min*ng/mL)	12	5	510	1366	2330	1403	32.36	1325
	AUC0-last (min*ng/mL)	12	5	406	1153	1990	1187	33.13	1117
	Cmax (ng/mL)	12	5	2.17	6.16	12.1	6.862	38.18	6.347
	T1/2(z) (min)	12	5	89.8	122.5	143	121.6	13.4	120.6
	Tmax (min)	12	5	30	60	61	57.58	15.09	56.71
ZYN® Smooth 6 mg (alt. manu. proc.)	AUC0-60 (min*ng/mL)	12	5	254	451.7	823	492.9	36.69	463.8
	AUC0-inf (min*ng/mL)	12	5	1310	2653	4590	2747	33.63	2602
	AUC0-last (min*ng/mL)	12	5	1120	2215	4020	2303	34.65	2177
	Cmax (ng/mL)	12	5	7.21	12.6	24	13.53	37.68	12.74
	T1/2(z) (min)	12	5	83.7	128.9	163	124.2	18.25	122.2
	Tmax (min)	12	5	60	60	90	65.08	17.89	64.28
Swedish portion snus PSWL 1.0 g (8 mg)	AUC0-60 (min*ng/mL)	12	5	147	363.7	572	379.7	32.9	358.2
	AUC0-inf (min*ng/mL)	12	5	1410	2159	3400	2135	26.57	2070
	AUC0-last (min*ng/mL)	12	5	1070	1860	2980	1808	28.18	1745
	Cmax (ng/mL)	12	5	5.45	9.96	15.4	10.05	27.08	9.702
	T1/2(z) (min)	12	5	98.4	120.3	157	121.6	15.22	120.4
	Tmax (min)	12	5	30	60	90	65.08	26.58	62.76

Min and max values have been rounded to three significant digits. STD, CV, mean, median and geometric mean have been rounded to 4 significant digits

SM17_03 PK parameter data, SAS program: pp_tabulations.sas. Run by: Lars Norberg, lars.norberg@ctc-ab.se 2019-06-25T09:11:50

*Table 14.3-101 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)*

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0002
Mean (Std)	1243.84 (430.62)	1808.35 (509.67)	-564.51 (356.66)	Signed Rank	0.0010
Median (min;max)	1162.48 (631.02;2290.78)	1860.1 (1070.65;2977.02)	-599.93 (-1103.02;133.16)		
Q1, Q3 (IQR)	1024.26 1406.56 (382.3)	1456.92 2107.51 (650.59)	-775.86 -309.89 (465.97)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-102 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1243.84 (430.62)	2541.01 (868.86)	-1297.18 (649.84)	Signed Rank	0.0005
Median (min;max)	1162.48 (631.02;2290.78)	2632.1 (1109.47;3961.1)	-1180.21 (-2434.91;-49.43)		
Q1, Q3 (IQR)	1024.26 1406.56 (382.3)	2152.76 2821.27 (668.51)	-1755.81 -1047.9 (707.91)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-103 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.2707
Mean (Std)	1243.84 (430.62)	1187.03 (393.23)	56.81 (169.68)	Signed Rank	0.1514
Median (min;max)	1162.48 (631.02;2290.78)	1153.18 (406.35;1991.34)	90.58 (-356.5;299.45)		
Q1, Q3 (IQR)	1024.26 1406.56 (382.3)	989.46 1396.59 (407.13)	-25.77 146.68 (172.45)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-104 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1243.84 (430.62)	2303.21 (798.06)	-1059.37 (543.77)	Signed Rank	0.0005
Median (min;max)	1162.48 (631.02;2290.78)	2214.8 (1120.45;4019.73)	-987.67 (-1790.95;-193.39)		
Q1, Q3 (IQR)	1024.26 1406.56 (382.3)	1820.83 2701.48 (880.65)	-1693.31 -685.92 (1007.39)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-105 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0017
Mean (Std)	2541.01 (868.86)	1808.35 (509.67)	732.67 (614.78)	Signed Rank	0.0024
Median (min;max)	2632.1 (1109.47;3961.1)	1860.1 (1070.65;2977.02)	787.54 (-322.58;1785.08)		
Q1, Q3 (IQR)	2152.76 2821.27 (668.51)	1456.92 2107.51 (650.59)	523.93 1098.94 (575.01)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-106 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	2541.01 (868.86)	1187.03 (393.23)	1353.98 (611.55)	Signed Rank	0.0005
Median (min;max)	2632.1 (1109.47;3961.1)	1153.18 (406.35;1991.34)	1282.91 (105.78;2451.41)		
Q1, Q3 (IQR)	2152.76 2821.27 (668.51)	989.46 1396.59 (407.13)	1111.62 1769.2 (657.58)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-107 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1189
Mean (Std)	2541.01 (868.86)	2303.21 (798.06)	237.81 (487.16)	Signed Rank	0.0923
Median (min;max)	2632.1 (1109.47;3961.1)	2214.8 (1120.45;4019.73)	190.23 (-757.57;1053.04)		
Q1, Q3 (IQR)	2152.76 2821.27 (668.51)	1820.83 2701.48 (880.65)	-34.8 579.61 (614.41)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-108 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1187.03 (393.23)	1808.35 (509.67)	-621.31 (342.34)	Signed Rank	0.0005
Median (min;max)	1153.18 (406.35;1991.34)	1860.1 (1070.65;2977.02)	-574.16 (-1174.26;-39.33)		
Q1, Q3 (IQR)	989.46 1396.59 (407.13)	1456.92 2107.51 (650.59)	-925.92 -375.93 (549.99)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-109 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1187.03 (393.23)	2303.21 (798.06)	-1116.17 (532.81)	Signed Rank	0.0005
Median (min;max)	1153.18 (406.35;1991.34)	2214.8 (1120.45;4019.73)	-935.57 (-2028.4;-249.75)		
Q1, Q3 (IQR)	989.46 1396.59 (407.13)	1820.83 2701.48 (880.65)	-1523.31 -794.58 (728.73)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-110 Difference in AUC_{0-t} (min*ng/mL): ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0181
Mean (Std)	2303.21 (798.06)	1808.35 (509.67)	494.86 (617.83)	Signed Rank	0.0210
Median (min;max)	2214.8 (1120.45;4019.73)	1860.1 (1070.65;2977.02)	554.16 (-451.72;1543.18)		
Q1, Q3 (IQR)	1820.83 2701.48 (880.65)	1456.92 2107.51 (650.59)	-89.07 971.79 (1060.86)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-111 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0045
Mean (Std)	272.92 (94.63)	379.68 (124.91)	-106.77 (104.09)	Signed Rank	0.0049
Median (min;max)	248.8 (160.94;463.45)	363.66 (146.66;572.03)	-102.27 (-317.37;77.48)		
Q1, Q3 (IQR)	202.45 345.88 (143.43)	298.36 492.58 (194.22)	-151.5 -47.2 (104.3)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-112 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	272.92 (94.63)	559.7 (195.11)	-286.78 (154.58)	Signed Rank	0.0005
Median (min;max)	248.8 (160.94;463.45)	522.77 (256.8;935.1)	-309.56 (-567.45;-14.83)		
Q1, Q3 (IQR)	202.45 345.88 (143.43)	476.47 630.07 (153.6)	-388.31 -167.07 (221.24)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-113 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.3071
Mean (Std)	272.92 (94.63)	254.66 (96.53)	18.26 (59.06)	Signed Rank	0.3804
Median (min;max)	248.8 (160.94;463.45)	234.44 (104.01;417.23)	10.99 (-82.3;127.47)		
Q1, Q3 (IQR)	202.45 345.88 (143.43)	186.06 315.31 (129.25)	-24.75 59.4 (84.15)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-114 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0003
Mean (Std)	272.92 (94.63)	492.94 (180.85)	-220.02 (146.03)	Signed Rank	0.0005
Median (min;max)	248.8 (160.94;463.45)	451.75 (254.26;823.43)	-234.01 (-523.68;-12.3)		
Q1, Q3 (IQR)	202.45 345.88 (143.43)	382.61 603.51 (220.9)	-283.71 -105.32 (178.39)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-115 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0022
Mean (Std)	559.7 (195.11)	379.68 (124.91)	180.02 (156.96)	Signed Rank	0.0068
Median (min;max)	522.77 (256.8;935.1)	363.66 (146.66;572.03)	178.67 (-41.37;434.33)		
Q1, Q3 (IQR)	476.47 630.07 (153.6)	298.36 492.58 (194.22)	55.12 289.84 (234.72)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-116 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	559.7 (195.11)	254.66 (96.53)	305.04 (164.02)	Signed Rank	0.0010
Median (min;max)	522.77 (256.8;935.1)	234.44 (104.01;417.23)	293.58 (-4.01;570.64)		
Q1, Q3 (IQR)	476.47 630.07 (153.6)	186.06 315.31 (129.25)	249.11 432.16 (183.05)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-117 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0855
Mean (Std)	559.7 (195.11)	492.94 (180.85)	66.76 (122.42)	Signed Rank	0.0771
Median (min;max)	522.77 (256.8;935.1)	451.75 (254.26;823.43)	70.63 (-178.45;274.1)		
Q1, Q3 (IQR)	476.47 630.07 (153.6)	382.61 603.51 (220.9)	17.86 141.58 (123.72)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-118 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0014
Mean (Std)	254.66 (96.53)	379.68 (124.91)	-125.03 (101.99)	Signed Rank	0.0015
Median (min;max)	234.44 (104.01;417.23)	363.66 (146.66;572.03)	-114.61 (-313.35;33.87)		
Q1, Q3 (IQR)	186.06 315.31 (129.25)	298.36 492.58 (194.22)	-162.85 -59.29 (103.56)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-119 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0003
Mean (Std)	254.66 (96.53)	492.94 (180.85)	-238.28 (159.57)	Signed Rank	0.0010
Median (min;max)	234.44 (104.01;417.23)	451.75 (254.26;823.43)	-230.74 (-606.23;6.54)		
Q1, Q3 (IQR)	186.06 315.31 (129.25)	382.61 603.51 (220.9)	-284.43 -162.04 (122.39)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-120 Difference in AUC₀₋₆₀ (min*ng/mL): ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0323
Mean (Std)	492.94 (180.85)	379.68 (124.91)	113.26 (160.15)	Signed Rank	0.0522
Median (min;max)	451.75 (254.26;823.43)	363.66 (146.66;572.03)	99.33 (-78.07;435.32)		
Q1, Q3 (IQR)	382.61 603.51 (220.9)	298.36 492.58 (194.22)	-29.53 205.81 (235.34)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-121 Difference in C_{max} (ng/mL): ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0008
Mean (Std)	7.1 (2.87)	10.05 (2.72)	-2.95 (2.23)	Signed Rank	0.0010
Median (min;max)	6.33 (3.52;13.8)	9.96 (5.45;15.4)	-2.23 (-6.88;0.7)		
Q1, Q3 (IQR)	5.5 8.76 (3.26)	8.27 11.8 (3.53)	-4.57 -1.62 (2.95)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-122 Difference in C_{max} (ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	7.1 (2.87)	15.04 (6.05)	-7.94 (4.18)	Signed Rank	0.0005
Median (min;max)	6.33 (3.52;13.8)	14.5 (6.02;27.8)	-7.76 (-14;-0.21)		
Q1, Q3 (IQR)	5.5 8.76 (3.26)	11.85 17.65 (5.8)	-11.83 -5.12 (6.71)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-123 Difference in C_{max} (ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.5437
Mean (Std)	7.1 (2.87)	6.86 (2.62)	0.24 (1.34)	Signed Rank	0.4229
Median (min;max)	6.33 (3.52;13.8)	6.16 (2.17;12.1)	0.23 (-2.5;2.65)		
Q1, Q3 (IQR)	5.5 8.76 (3.26)	5.74 8.67 (2.93)	-0.22 0.96 (1.18)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-124 Difference in C_{max} (ng/mL): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	7.1 (2.87)	13.53 (5.1)	-6.43 (3.74)	Signed Rank	0.0005
Median (min;max)	6.33 (3.52;13.8)	12.6 (7.21;24)	-5.68 (-14.86;-1.4)		
Q1, Q3 (IQR)	5.5 8.76 (3.26)	10.15 15.3 (5.15)	-8.4 -3.83 (4.57)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-125 Difference in C_{max} (ng/mL): ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0017
Mean (Std)	15.04 (6.05)	10.05 (2.72)	4.99 (4.18)	Signed Rank	0.0049
Median (min;max)	14.5 (6.02;27.8)	9.96 (5.45;15.4)	5.46 (-1.29;12.4)		
Q1, Q3 (IQR)	11.85 17.65 (5.8)	8.27 11.8 (3.53)	2.05 6.68 (4.63)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-126 Difference in C_{max} (ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	15.04 (6.05)	6.86 (2.62)	8.18 (4.16)	Signed Rank	0.0005
Median (min;max)	14.5 (6.02;27.8)	6.16 (2.17;12.1)	8.11 (0.48;15.7)		
Q1, Q3 (IQR)	11.85 17.65 (5.8)	5.74 8.67 (2.93)	5.34 11.07 (5.73)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-127 Difference in C_{max} (ng/mL): ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1875
Mean (Std)	15.04 (6.05)	13.53 (5.1)	1.51 (3.71)	Signed Rank	0.1763
Median (min;max)	14.5 (6.02;27.8)	12.6 (7.21;24)	1.75 (-7.4;6.1)		
Q1, Q3 (IQR)	11.85 17.65 (5.8)	10.15 15.3 (5.15)	-0.42 4.1 (4.52)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-128 Difference in C_{max} (ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0002
Mean (Std)	6.86 (2.62)	10.05 (2.72)	-3.19 (2.06)	Signed Rank	0.0010
Median (min;max)	6.16 (2.17;12.1)	9.96 (5.45;15.4)	-2.82 (-6.72;0.48)		
Q1, Q3 (IQR)	5.74 8.67 (2.93)	8.27 11.8 (3.53)	-4.36 -1.88 (2.48)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-129 Difference in C_{max} (ng/mL): ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0002
Mean (Std)	6.86 (2.62)	13.53 (5.1)	-6.67 (4.29)	Signed Rank	0.0005
Median (min;max)	6.16 (2.17;12.1)	12.6 (7.21;24)	-5.76 (-17.51;-1.67)		
Q1, Q3 (IQR)	5.74 8.67 (2.93)	10.15 15.3 (5.15)	-7.41 -3.8 (3.61)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-130 Difference C_{max} (ng/mL): ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0125
Mean (Std)	13.53 (5.1)	10.05 (2.72)	3.48 (4.05)	Signed Rank	0.0122
Median (min;max)	12.6 (7.21;24)	9.96 (5.45;15.4)	3.4 (-0.6;13.02)		
Q1, Q3 (IQR)	10.15 15.3 (5.15)	8.27 11.8 (3.53)	0.02 4.48 (4.46)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-131 Difference in terminal half-life (min): ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1647
Mean (Std)	132.73 (25.84)	121.65 (18.51)	11.08 (25.8)	Signed Rank	0.1514
Median (min;max)	125.04 (96.27;174.68)	120.3 (98.36;157)	7.71 (-40.94;52.9)		
Q1, Q3 (IQR)	112.47 155.89 (43.42)	107 135.62 (28.62)	-1.55 24.17 (25.72)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-132 Difference in terminal half-life (min): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1077
Mean (Std)	132.73 (25.84)	118.71 (25.29)	14.02 (27.74)	Signed Rank	0.0640
Median (min;max)	125.04 (96.27;174.68)	122.6 (70.71;158.63)	14.76 (-45.35;62.25)		
Q1, Q3 (IQR)	112.47 155.89 (43.42)	101.12 133.78 (32.66)	-0.65 26.04 (26.69)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-133 Difference in terminal half-life (min): ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0623
Mean (Std)	132.73 (25.84)	121.63 (16.3)	11.11 (18.55)	Signed Rank	0.0640
Median (min;max)	125.04 (96.27;174.68)	122.47 (89.78;143.18)	9.19 (-18.63;52.03)		
Q1, Q3 (IQR)	112.47 155.89 (43.42)	113.12 133.03 (19.91)	-0.65 22.64 (23.29)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-134 Difference in terminal half-life (min): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.2283
Mean (Std)	132.73 (25.84)	124.25 (22.67)	8.49 (23.04)	Signed Rank	0.3394
Median (min;max)	125.04 (96.27;174.68)	128.95 (83.72;163.21)	5.92 (-21.14;49.57)		
Q1, Q3 (IQR)	112.47 155.89 (43.42)	108.25 137.27 (29.02)	-9.53 21.06 (30.59)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-135 Difference in terminal half-life (min): ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6948
Mean (Std)	118.71 (25.29)	121.65 (18.51)	-2.94 (25.26)	Signed Rank	0.4238
Median (min;max)	122.6 (70.71;158.63)	120.3 (98.36;157)	-5.63 (-35.54;58.48)		
Q1, Q3 (IQR)	101.12 133.78 (32.66)	107 135.62 (28.62)	-20.89 4.45 (25.34)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-136 Difference in terminal half-life (min): ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6507
Mean (Std)	118.71 (25.29)	121.63 (16.3)	-2.91 (21.69)	Signed Rank	0.5693
Median (min;max)	122.6 (70.71;158.63)	122.47 (89.78;143.18)	-0.45 (-35.45;46.65)		
Q1, Q3 (IQR)	101.12 133.78 (32.66)	113.12 133.03 (19.91)	-20.44 7.88 (28.32)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-137 Difference in terminal half-life (min): ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.2404
Mean (Std)	118.71 (25.29)	124.25 (22.67)	-5.54 (15.45)	Signed Rank	0.2334
Median (min;max)	122.6 (70.71;158.63)	128.95 (83.72;163.21)	-9.14 (-25.04;24.87)		
Q1, Q3 (IQR)	101.12 133.78 (32.66)	108.25 137.27 (29.02)	-15.27 2.04 (17.31)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-138 Difference in terminal half-life (min): ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.9954
Mean (Std)	121.63 (16.3)	121.65 (18.51)	-0.02 (13.23)	Signed Rank	0.9097
Median (min;max)	122.47 (89.78;143.18)	120.3 (98.36;157)	-1.56 (-22.31;26.1)		
Q1, Q3 (IQR)	113.12 133.03 (19.91)	107 135.62 (28.62)	-9.73 8.9 (18.63)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-139 Difference in terminal half-life (min): ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.5649
Mean (Std)	121.63 (16.3)	124.25 (22.67)	-2.62 (15.3)	Signed Rank	0.7334
Median (min;max)	122.47 (89.78;143.18)	128.95 (83.72;163.21)	-4.81 (-31.96;22.77)		
Q1, Q3 (IQR)	113.12 133.03 (19.91)	108.25 137.27 (29.02)	-7.82 10.04 (17.86)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-140 Difference in terminal half-life (min): ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6253
Mean (Std)	124.25 (22.67)	121.65 (18.51)	2.6 (17.92)	Signed Rank	0.5693
Median (min;max)	128.95 (83.72;163.21)	120.3 (98.36;157)	3.96 (-26.94;33.61)		
Q1, Q3 (IQR)	108.25 137.27 (29.02)	107 135.62 (28.62)	-10.28 14.65 (24.93)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-141 Difference in T_{max} (min): ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.4708
Mean (Std)	60.42 (12.83)	65.08 (17.3)	-4.67 (21.64)	Signed Rank	0.6289
Median (min;max)	60 (30;90)	60 (30;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 61 (1)	60 75.5 (15.5)	-30 2.5 (32.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-142 Difference in T_{max} (min): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1447
Mean (Std)	60.42 (12.83)	56.25 (12.99)	4.17 (9.19)	Signed Rank	0.1250
Median (min;max)	60 (30;90)	60 (15;60)	0 (0;30)		
Q1, Q3 (IQR)	60 61 (1)	60 60 (0)	0 2.5 (2.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-143 Difference in T_{max} (min): ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6339
Mean (Std)	60.42 (12.83)	57.58 (8.69)	2.83 (20.04)	Signed Rank	0.6250
Median (min;max)	60 (30;90)	60 (30;61)	0 (-30;60)		
Q1, Q3 (IQR)	60 61 (1)	60 60 (0)	0 1 (1)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-144 Difference in T_{max} (min): ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.3743
Mean (Std)	60.42 (12.83)	65.08 (11.64)	-4.67 (17.46)	Signed Rank	0.5625
Median (min;max)	60 (30;90)	60 (60;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 61 (1)	60 60.5 (0.5)	-15.5 1 (16.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-145 Difference in T_{max} (min): ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1664
Mean (Std)	56.25 (12.99)	65.08 (17.3)	-8.83 (20.65)	Signed Rank	0.1875
Median (min;max)	60 (15;60)	60 (30;90)	0 (-45;30)		
Q1, Q3 (IQR)	60 60 (0)	60 75.5 (15.5)	-30 0 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-146 Difference in T_{max} (min): ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.7815
Mean (Std)	56.25 (12.99)	57.58 (8.69)	-1.33 (16.25)	Signed Rank	0.7500
Median (min;max)	60 (15;60)	60 (30;61)	0 (-45;30)		
Q1, Q3 (IQR)	60 60 (0)	60 60 (0)	0 0 (0)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-147 Difference in T_{max} (min): ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0857
Mean (Std)	56.25 (12.99)	65.08 (11.64)	-8.83 (16.21)	Signed Rank	0.1250
Median (min;max)	60 (15;60)	60 (60;90)	0 (-45;0)		
Q1, Q3 (IQR)	60 60 (0)	60 60.5 (0.5)	-15.5 0 (15.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-148 Difference in T_{max} (min): ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1944
Mean (Std)	57.58 (8.69)	65.08 (17.3)	-7.5 (18.8)	Signed Rank	0.3438
Median (min;max)	60 (30;61)	60 (30;90)	0 (-30;31)		
Q1, Q3 (IQR)	60 60 (0)	60 75.5 (15.5)	-30 0 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-149 Difference in T_{max} (min): ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0820
Mean (Std)	57.58 (8.69)	65.08 (11.64)	-7.5 (13.57)	Signed Rank	0.1875
Median (min;max)	60 (30;61)	60 (60;90)	0 (-30;1)		
Q1, Q3 (IQR)	60 60 (0)	60 60.5 (0.5)	-15.5 0 (15.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

Table 14.3-150 Difference in T_{max} (min): ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	1.0000
Mean (Std)	65.08 (11.64)	65.08 (17.3)	0 (18.1)	Signed Rank	1.0000
Median (min;max)	60 (60;90)	60 (30;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 60.5 (0.5)	60 75.5 (15.5)	-0.5 0.5 (1)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:58

14.3.2.8 Difference in pharmacokinetic parameters (baseline adjusted data, N=12)

Table 14.3-151 Pharmacokinetic parameters by treatment (baseline adjusted data)

Name of Actual Treatment	Analyte (unit)	N	NMiss	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN® Smooth 3 mg	AUC0-60 (min*ng/mL)	12	5	127	192.4	408	225.5	41.99	209.4
	AUC0-inf (min*ng/mL)	12	5	695	1215	2510	1323	35.89	1254
	AUC0-last (min*ng/mL)	12	5	529	1040	2130	1095	38.76	1027
	Cmax (ng/mL)	12	5	3.04	5.671	13	6.442	44.54	5.92
	T1/2(z) (min)	12	5	96.3	125	175	132.7	19.47	130.5
	Tmax (min)	12	5	30	60	90	60.42	21.24	58.98
ZYN® Smooth 6 mg	AUC0-60 (min*ng/mL)	12	5	208	478.3	866	521.2	36.77	488.9
	AUC0-inf (min*ng/mL)	12	5	1240	3008	4630	2847	35.87	2655
	AUC0-last (min*ng/mL)	12	5	1010	2489	3880	2422	35.05	2264
	Cmax (ng/mL)	12	5	5.33	14.03	27.4	14.5	41.68	13.3
	T1/2(z) (min)	12	5	70.7	122.6	159	118.7	21.3	116.1
	Tmax (min)	12	5	15	60	60	56.25	23.09	53.45
ZYN® Smooth 3 mg (alt. manu. proc.)	AUC0-60 (min*ng/mL)	12	5	104	195.4	358	216.3	38.68	201.9
	AUC0-inf (min*ng/mL)	12	5	510	1233	2130	1266	31.54	1203
	AUC0-last (min*ng/mL)	12	5	406	1024	1820	1069	33.14	1010
	Cmax (ng/mL)	12	5	2.17	5.705	11.3	6.305	40.09	5.82
	T1/2(z) (min)	12	5	89.8	122.5	143	121.6	13.39	120.5
	Tmax (min)	12	5	30	60	61	57.58	15.09	56.71
ZYN® Smooth 6 mg (alt. manu. proc.)	AUC0-60 (min*ng/mL)	12	5	161	422.1	774	444.4	40.92	408.2
	AUC0-inf (min*ng/mL)	12	5	1200	2547	4440	2569	35.91	2411
	AUC0-last (min*ng/mL)	12	5	987	2128	3880	2153	37.28	2010
	Cmax (ng/mL)	12	5	5.84	12.34	23.3	12.87	39.68	12.01
	T1/2(z) (min)	12	5	83.7	128.9	163	124.2	18.24	122.2
	Tmax (min)	12	5	60	60	90	65.08	17.89	64.28
Swedish portion snus PSWL 1.0 g (8 mg)	AUC0-60 (min*ng/mL)	12	5	147	343.8	500	342.3	33.71	322.4
	AUC0-inf (min*ng/mL)	12	5	1330	2066	3170	2007	26.22	1947
	AUC0-last (min*ng/mL)	12	5	1070	1759	2770	1697	28	1638
	Cmax (ng/mL)	12	5	5.45	9.387	14.6	9.546	27.35	9.208
	T1/2(z) (min)	12	5	98.4	120.3	157	121.6	15.23	120.4
	Tmax (min)	12	5	30	60	90	67.5	27.63	64.83

Min and max values have been rounded to three significant digits. STD, CV, mean, median and geometric mean have been rounded to 4 significant digits

SM17_03 PK parameter data, SAS program: pp_tabulations.sas. Run by: Lars Norberg, lars.norberg@ctc-ab.se 2019-06-25T09:11:50

Table 14.3-152 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1094.6 (424.28)	1696.83 (475.09)	-602.23 (331.28)	Signed Rank	0.0010
Median (min;max)	1040.15 (528.98;2134.14)	1759.02 (1070.65;2772.9)	-617.08 (-1127.4;37.67)		
Q1, Q3 (IQR)	825.54 1283.96 (458.42)	1348.25 1968.52 (620.27)	-853.08 -372.83 (480.25)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-153 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1094.6 (424.28)	2422.22 (848.87)	-1327.62 (609.24)	Signed Rank	0.0005
Median (min;max)	1040.15 (528.98;2134.14)	2489.24 (1014.23;3884.85)	-1216.58 (-2302.58;-160)		
Q1, Q3 (IQR)	825.54 1283.96 (458.42)	2014.27 2728.69 (714.42)	-1822.2 -1045.42 (776.78)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-154 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6311
Mean (Std)	1094.6 (424.28)	1069.15 (354.27)	25.45 (178.52)	Signed Rank	0.5186
Median (min;max)	1040.15 (528.98;2134.14)	1023.91 (406.35;1819.79)	33.25 (-351.19;314.34)		
Q1, Q3 (IQR)	825.54 1283.96 (458.42)	908.92 1311.29 (402.37)	-82.3 149.44 (231.74)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-155 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1094.6 (424.28)	2152.64 (802.6)	-1058.04 (539.1)	Signed Rank	0.0005
Median (min;max)	1040.15 (528.98;2134.14)	2127.79 (987.12;3881.32)	-1023.19 (-1820.06;-132.89)		
Q1, Q3 (IQR)	825.54 1283.96 (458.42)	1729.71 2545.35 (815.64)	-1608.4 -689.57 (918.83)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-156 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0014
Mean (Std)	2422.22 (848.87)	1696.83 (475.09)	725.39 (591.83)	Signed Rank	0.0024
Median (min;max)	2489.24 (1014.23;3884.85)	1759.02 (1070.65;2772.9)	786.15 (-311.22;1688.5)		
Q1, Q3 (IQR)	2014.27 2728.69 (714.42)	1348.25 1968.52 (620.27)	499.31 1074.91 (575.6)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-157 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	2422.22 (848.87)	1069.15 (354.27)	1353.07 (588.51)	Signed Rank	0.0005
Median (min;max)	2489.24 (1014.23;3884.85)	1023.91 (406.35;1819.79)	1300.38 (133.51;2308.39)		
Q1, Q3 (IQR)	2014.27 2728.69 (714.42)	908.92 1311.29 (402.37)	1124.55 1731.52 (606.97)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-158 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0729
Mean (Std)	2422.22 (848.87)	2152.64 (802.6)	269.58 (471.02)	Signed Rank	0.0161
Median (min;max)	2489.24 (1014.23;3884.85)	2127.79 (987.12;3881.32)	187.39 (-696.88;1059.41)		
Q1, Q3 (IQR)	2014.27 2728.69 (714.42)	1729.71 2545.35 (815.64)	40.83 570.61 (529.78)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-159 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1069.15 (354.27)	1696.83 (475.09)	-627.68 (309.67)	Signed Rank	0.0005
Median (min;max)	1023.91 (406.35;1819.79)	1759.02 (1070.65;2772.9)	-550.93 (-1035.69;-133.53)		
Q1, Q3 (IQR)	908.92 1311.29 (402.37)	1348.25 1968.52 (620.27)	-958.72 -384.52 (574.2)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-160 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	1069.15 (354.27)	2152.64 (802.6)	-1083.49 (553.1)	Signed Rank	0.0005
Median (min;max)	1023.91 (406.35;1819.79)	2127.79 (987.12;3881.32)	-944.15 (-2061.53;-106.4)		
Q1, Q3 (IQR)	908.92 1311.29 (402.37)	1729.71 2545.35 (815.64)	-1435.72 -738.68 (697.04)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-161 Difference in AUC_{0-t} (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0280
Mean (Std)	2152.64 (802.6)	1696.83 (475.09)	455.81 (624.05)	Signed Rank	0.0210
Median (min;max)	2127.79 (987.12;3881.32)	1759.02 (1070.65;2772.9)	495.41 (-410.46;1502.89)		
Q1, Q3 (IQR)	1729.71 2545.35 (815.64)	1348.25 1968.52 (620.27)	-160.54 892.76 (1053.3)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-162 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0014
Mean (Std)	225.46 (94.68)	342.28 (115.37)	-116.82 (95.85)	Signed Rank	0.0015
Median (min;max)	192.41 (127.5;408.26)	343.81 (146.66;499.67)	-110.21 (-300.08;44.91)		
Q1, Q3 (IQR)	155.86 293.49 (137.63)	248.45 441.12 (192.67)	-161.41 -60.8 (100.61)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by:
Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-163 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	225.46 (94.68)	521.21 (191.67)	-295.75 (144.06)	Signed Rank	0.0005
Median (min;max)	192.41 (127.5;408.26)	478.32 (208.15;866.43)	-293.86 (-534.59;-44.26)		
Q1, Q3 (IQR)	155.86 293.49 (137.63)	419.42 594.67 (175.25)	-404.29 -186.64 (217.65)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by:
Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-164 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.5610
Mean (Std)	225.46 (94.68)	216.34 (83.68)	9.12 (52.7)	Signed Rank	0.6221
Median (min;max)	192.41 (127.5;408.26)	195.45 (104.01;358.3)	17.71 (-61.29;100.91)		
Q1, Q3 (IQR)	155.86 293.49 (137.63)	151.13 291.24 (140.11)	-36.72 46.9 (83.62)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by:
Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-165 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0003
Mean (Std)	225.46 (94.68)	444.39 (181.86)	-218.93 (144.84)	Signed Rank	0.0010
Median (min;max)	192.41 (127.5;408.26)	422.12 (160.53;774.1)	-239.11 (-529.08;3.36)		
Q1, Q3 (IQR)	155.86 293.49 (137.63)	338.66 541.6 (202.94)	-255.84 -117.07 (138.77)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by:
Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-166 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0018
Mean (Std)	521.21 (191.67)	342.28 (115.37)	178.93 (152.1)	Signed Rank	0.0068
Median (min;max)	478.32 (208.15;866.43)	343.81 (146.66;499.67)	168.1 (-41.37;417.32)		
Q1, Q3 (IQR)	419.42 594.67 (175.25)	248.45 441.12 (192.67)	59.16 288.21 (229.05)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by:
Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-167 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	521.21 (191.67)	216.34 (83.68)	304.87 (153.03)	Signed Rank	0.0005

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
Median (min;max)	478.32 (208.15;866.43)	195.45 (104.01;358.3)	297.96 (6.03;534.3)		
Q1, Q3 (IQR)	419.42 594.67 (175.25)	151.13 291.24 (140.11)	257.66 415.35 (157.69)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

*Table 14.3-168 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)*

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0492
Mean (Std)	521.21 (191.67)	444.39 (181.86)	76.82 (120.41)	Signed Rank	0.0640
Median (min;max)	478.32 (208.15;866.43)	422.12 (160.53;774.1)	68.6 (-159.16;281.84)		
Q1, Q3 (IQR)	419.42 594.67 (175.25)	338.66 541.6 (202.94)	42.74 153.37 (110.63)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

*Table 14.3-169 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)*

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0005
Mean (Std)	216.34 (83.68)	342.28 (115.37)	-125.94 (88.51)	Signed Rank	0.0010
Median (min;max)	195.45 (104.01;358.3)	343.81 (146.66;499.67)	-117.07 (-300.76;4.21)		
Q1, Q3 (IQR)	151.13 291.24 (140.11)	248.45 441.12 (192.67)	-154.88 -70.39 (84.49)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

*Table 14.3-170 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)*

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0004
Mean (Std)	216.34 (83.68)	444.39 (181.86)	-228.05 (157.65)	Signed Rank	0.0010
Median (min;max)	195.45 (104.01;358.3)	422.12 (160.53;774.1)	-194.78 (-586.43;41.58)		
Q1, Q3 (IQR)	151.13 291.24 (140.11)	338.66 541.6 (202.94)	-263.96 -183.38 (80.58)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

*Table 14.3-171 Difference in AUC₀₋₆₀ (min*ng/mL), with baseline adjustment: ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)*

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0503
Mean (Std)	444.39 (181.86)	342.28 (115.37)	102.11 (160.98)	Signed Rank	0.0771
Median (min;max)	422.12 (160.53;774.1)	343.81 (146.66;499.67)	90.7 (-106.36;418.04)		
Q1, Q3 (IQR)	338.66 541.6 (202.94)	248.45 441.12 (192.67)	-47.6 208.23 (255.83)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-172 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0004
Mean (Std)	6.44 (2.87)	9.55 (2.61)	-3.1 (2.15)	Signed Rank	0.0010
Median (min;max)	5.67 (3.04;13.04)	9.39 (5.45;14.58)	-2.43 (-6.5;0.25)		
Q1, Q3 (IQR)	4.51 8.17 (3.66)	7.93 11.45 (3.52)	-4.95 -1.63 (3.32)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-173 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	6.44 (2.87)	14.5 (6.04)	-8.06 (4.08)	Signed Rank	0.0005
Median (min;max)	5.67 (3.04;13.04)	14.03 (5.33;27.41)	-8.12 (-14.37;-0.64)		
Q1, Q3 (IQR)	4.51 8.17 (3.66)	11.02 17.43 (6.41)	-11.79 -5.11 (6.68)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-174 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.7231
Mean (Std)	6.44 (2.87)	6.3 (2.53)	0.14 (1.31)	Signed Rank	0.7910
Median (min;max)	5.67 (3.04;13.04)	5.71 (2.17;11.29)	0.08 (-2.42;2.31)		
Q1, Q3 (IQR)	4.51 8.17 (3.66)	5.08 7.92 (2.84)	-0.52 1.05 (1.57)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-175 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	6.44 (2.87)	12.87 (5.11)	-6.42 (3.74)	Signed Rank	0.0005
Median (min;max)	5.67 (3.04;13.04)	12.34 (5.84;23.33)	-5.64 (-14.94;-1.15)		
Q1, Q3 (IQR)	4.51 8.17 (3.66)	9.63 14.47 (4.84)	-8.34 -4.06 (4.28)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-176 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0018
Mean (Std)	14.5 (6.04)	9.55 (2.61)	4.95 (4.2)	Signed Rank	0.0049
Median (min;max)	14.03 (5.33;27.41)	9.39 (5.45;14.58)	5.66 (-1.29;12.82)		
Q1, Q3 (IQR)	11.02 17.43 (6.41)	7.93 11.45 (3.52)	1.85 6.33 (4.48)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-177 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	<.0001
Mean (Std)	14.5 (6.04)	6.3 (2.53)	8.19 (4.09)	Signed Rank	0.0005
Median (min;max)	14.03 (5.33;27.41)	5.71 (2.17;11.29)	8.15 (0.62;16.12)		
Q1, Q3 (IQR)	11.02 17.43 (6.41)	5.08 7.92 (2.84)	5.53 10.85 (5.32)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-178 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1483
Mean (Std)	14.5 (6.04)	12.87 (5.11)	1.63 (3.64)	Signed Rank	0.0923
Median (min;max)	14.03 (5.33;27.41)	12.34 (5.84;23.33)	1.55 (-7.13;6.18)		
Q1, Q3 (IQR)	11.02 17.43 (6.41)	9.63 14.47 (4.84)	-0.18 4.24 (4.42)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-179 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0001
Mean (Std)	6.3 (2.53)	9.55 (2.61)	-3.24 (1.9)	Signed Rank	0.0010
Median (min;max)	5.71 (2.17;11.29)	9.39 (5.45;14.58)	-2.98 (-6.27;0.06)		
Q1, Q3 (IQR)	5.08 7.92 (2.84)	7.93 11.45 (3.52)	-4.6 -1.95 (2.65)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-180 Difference in C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0003
Mean (Std)	6.3 (2.53)	12.87 (5.11)	-6.56 (4.29)	Signed Rank	0.0005
Median (min;max)	5.71 (2.17;11.29)	12.34 (5.84;23.33)	-5.74 (-17.25;-1.13)		
Q1, Q3 (IQR)	5.08 7.92 (2.84)	9.63 14.47 (4.84)	-7.09 -4.04 (3.05)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-181 Difference C_{max} (ng/mL), with baseline adjustment: ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0162
Mean (Std)	12.87 (5.11)	9.55 (2.61)	3.32 (4.06)	Signed Rank	0.0210
Median (min;max)	12.34 (5.84;23.33)	9.39 (5.45;14.58)	3.27 (-0.69;12.8)		
Q1, Q3 (IQR)	9.63 14.47 (4.84)	7.93 11.45 (3.52)	-0.18 4.09 (4.27)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-182 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1645
Mean (Std)	132.72 (25.84)	121.62 (18.53)	11.09 (25.8)	Signed Rank	0.1514
Median (min;max)	125.04 (96.26;174.68)	120.3 (98.36;157)	7.7 (-40.94;52.84)		
Q1, Q3 (IQR)	112.47 155.87 (43.4)	106.91 135.61 (28.7)	-1.57 24.23 (25.8)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-183 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1079
Mean (Std)	132.72 (25.84)	118.71 (25.29)	14.01 (27.73)	Signed Rank	0.0640
Median (min;max)	125.04 (96.26;174.68)	122.59 (70.71;158.63)	14.73 (-45.35;62.2)		
Q1, Q3 (IQR)	112.47 155.87 (43.4)	101.11 133.77 (32.66)	-0.65 26.04 (26.69)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-184 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0622
Mean (Std)	132.72 (25.84)	121.61 (16.29)	11.11 (18.54)	Signed Rank	0.0640
Median (min;max)	125.04 (96.26;174.68)	122.47 (89.78;143.18)	9.17 (-18.6;52.03)		
Q1, Q3 (IQR)	112.47 155.87 (43.4)	113.11 133 (19.89)	-0.64 22.63 (23.27)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-185 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.2278
Mean (Std)	132.72 (25.84)	124.23 (22.65)	8.49 (23.03)	Signed Rank	0.3394
Median (min;max)	125.04 (96.26;174.68)	128.95 (83.7;163.06)	5.92 (-21.14;49.57)		
Q1, Q3 (IQR)	112.47 155.87 (43.4)	108.25 137.26 (29.01)	-9.47 21.05 (30.52)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-186 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6970
Mean (Std)	118.71 (25.29)	121.62 (18.53)	-2.92 (25.27)	Signed Rank	0.4238
Median (min;max)	122.59 (70.71;158.63)	120.3 (98.36;157)	-5.62 (-35.55;58.49)		
Q1, Q3 (IQR)	101.11 133.77 (32.66)	106.91 135.61 (28.7)	-20.87 4.45 (25.32)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-187 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6520
Mean (Std)	118.71 (25.29)	121.61 (16.29)	-2.9 (21.69)	Signed Rank	0.5693
Median (min;max)	122.59 (70.71;158.63)	122.47 (89.78;143.18)	-0.45 (-35.45;46.65)		
Q1, Q3 (IQR)	101.11 133.77 (32.66)	113.11 133 (19.89)	-20.42 7.9 (28.32)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-188 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.2415
Mean (Std)	118.71 (25.29)	124.23 (22.65)	-5.52 (15.44)	Signed Rank	0.2661
Median (min;max)	122.59 (70.71;158.63)	128.95 (83.7;163.06)	-9.15 (-24.89;24.89)		
Q1, Q3 (IQR)	101.11 133.77 (32.66)	108.25 137.26 (29.01)	-15.28 2.05 (17.33)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-189 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.9971
Mean (Std)	121.61 (16.29)	121.62 (18.53)	-0.01 (13.25)	Signed Rank	0.9097
Median (min;max)	122.47 (89.78;143.18)	120.3 (98.36;157)	-1.58 (-22.34;26.1)		
Q1, Q3 (IQR)	113.11 133 (19.89)	106.91 135.61 (28.7)	-9.75 8.89 (18.64)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-190 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.5655
Mean (Std)	121.61 (16.29)	124.23 (22.65)	-2.62 (15.29)	Signed Rank	0.7334
Median (min;max)	122.47 (89.78;143.18)	128.95 (83.7;163.06)	-4.81 (-31.87;22.82)		
Q1, Q3 (IQR)	113.11 133 (19.89)	108.25 137.26 (29.01)	-7.84 10.02 (17.86)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-191 Difference in terminal half-life (min), with baseline adjustment: ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6250
Mean (Std)	124.23 (22.65)	121.62 (18.53)	2.6 (17.92)	Signed Rank	0.5693
Median (min;max)	128.95 (83.7;163.06)	120.3 (98.36;157)	3.94 (-26.95;33.6)		
Q1, Q3 (IQR)	108.25 137.26 (29.01)	106.91 135.61 (28.7)	-10.25 14.58 (24.83)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-192 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 3 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.3046
Mean (Std)	60.42 (12.83)	67.5 (18.65)	-7.08 (22.79)	Signed Rank	0.4531
Median (min;max)	60 (30;90)	60 (30;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 61 (1)	60 90 (30)	-30 2.5 (32.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-193 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg

Statistics	ZS3	ZS6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1447
Mean (Std)	60.42 (12.83)	56.25 (12.99)	4.17 (9.19)	Signed Rank	0.1250
Median (min;max)	60 (30;90)	60 (15;60)	0 (0;30)		
Q1, Q3 (IQR)	60 61 (1)	60 60 (0)	0 2.5 (2.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-194 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS3	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6339
Mean (Std)	60.42 (12.83)	57.58 (8.69)	2.83 (20.04)	Signed Rank	0.6250
Median (min;max)	60 (30;90)	60 (30;61)	0 (-30;60)		
Q1, Q3 (IQR)	60 61 (1)	60 60 (0)	0 1 (1)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-195 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 3 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.3743
Mean (Std)	60.42 (12.83)	65.08 (11.64)	-4.67 (17.46)	Signed Rank	0.5625
Median (min;max)	60 (30;90)	60 (60;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 61 (1)	60 60.5 (0.5)	-15.5 1 (16.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-196 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 6 mg vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZS6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0950
Mean (Std)	56.25 (12.99)	67.5 (18.65)	-11.25 (21.33)	Signed Rank	0.1875
Median (min;max)	60 (15;60)	60 (30;90)	0 (-45;30)		
Q1, Q3 (IQR)	60 60 (0)	60 90 (30)	-30 0 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-197 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 3 mg (alt. manu. proc.)

Statistics	ZS6	ZSA3	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.7815
Mean (Std)	56.25 (12.99)	57.58 (8.69)	-1.33 (16.25)	Signed Rank	0.7500
Median (min;max)	60 (15;60)	60 (30;61)	0 (-45;30)		
Q1, Q3 (IQR)	60 60 (0)	60 60 (0)	0 0 (0)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-198 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 6 mg vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZS6	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0857
Mean (Std)	56.25 (12.99)	65.08 (11.64)	-8.83 (16.21)	Signed Rank	0.1250
Median (min;max)	60 (15;60)	60 (60;90)	0 (-45;0)		
Q1, Q3 (IQR)	60 60 (0)	60 60.5 (0.5)	-15.5 0 (15.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-199 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA3	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.1095
Mean (Std)	57.58 (8.69)	67.5 (18.65)	-9.92 (19.73)	Signed Rank	0.5313
Median (min;max)	60 (30;61)	60 (30;90)	0 (-30;31)		
Q1, Q3 (IQR)	60 60 (0)	60 90 (30)	-30 0 (30)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-200 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 3 mg (alt. manu. proc.) vs. ZYN Smooth 6 mg (alt. manu. proc.)

Statistics	ZSA3	ZSA6	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.0820
Mean (Std)	57.58 (8.69)	65.08 (11.64)	-7.5 (13.57)	Signed Rank	0.1875
Median (min;max)	60 (30;61)	60 (60;90)	0 (-30;1)		
Q1, Q3 (IQR)	60 60 (0)	60 60.5 (0.5)	-15.5 0 (15.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

Table 14.3-201 Difference in T_{max} (min), with baseline adjustment: ZYN Smooth 6 mg (alt. manu. proc.) vs. Swedish portion snus PSWL 1.0 g (8 mg)

Statistics	ZSA6	PSWL	Difference between products	Statistical test	P-value
n (nmiss)	12 (5)	12 (5)	12 (5)	Student's t	0.6846
Mean (Std)	65.08 (11.64)	67.5 (18.65)	-2.42 (20.07)	Signed Rank	1.0000
Median (min;max)	60 (60;90)	60 (30;90)	0 (-30;30)		
Q1, Q3 (IQR)	60 60.5 (0.5)	60 90 (30)	-15 0.5 (15.5)		

SM17_03 Analysis of secondary endpoint - PK, SAS program: AUC_table_with_bsl.sas. Run by: Linnea Eriksson, linnea.eriksson@ctc-ab.se 2019-06-25T16:10:04

14.3.2.9 Vital signs

Table 14.3-202 Change in pulse rate (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN[®] Smooth 3 mg

Time point (min)	Statistics	PSWL	ZS3	Change in PSWL	Change in ZS3	Change in PSWL - Change in ZS3	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	63.71 (10.82)	62.88 (7.18)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	61 (51;98)	62 (50;74)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	59 67 (8)	58 70 (12)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3903
	Mean (Std)	64.71 (5.71)	65.94 (7.44)	1 (6.38)	3.06 (6.3)	-2.06 (9.61)	Signed Rank	0.5351
	Median (min;max)	64 (58;78)	65 (54;82)	1 (-20;9)	2 (-7;19)	-1 (-23;16)		
	Q1, Q3 (IQR)	60 69 (9)	61 71 (10)	0 4 (4)	-1 6 (7)	-5 5 (10)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6394
	Mean (Std)	69 (9.95)	67.06 (6.76)	5.29 (8.99)	4.18 (6.04)	1.12 (9.65)	Signed Rank	0.6025
	Median (min;max)	66 (54;87)	65 (56;81)	3 (-17;19)	5 (-13;14)	3 (-22;15)		
	Q1, Q3 (IQR)	62 79 (17)	63 72 (9)	1 13 (12)	2 7 (5)	-5 8 (13)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.9184
	Mean (Std)	70.06 (9.34)	68.94 (6.81)	6.35 (8.84)	6.06 (6.08)	0.29 (11.66)	Signed Rank	0.5863
	Median (min;max)	68 (55;87)	68 (60;81)	6 (-11;20)	5 (-8;21)	2 (-25;17)		
	Q1, Q3 (IQR)	66 73 (7)	63 74 (11)	2 11 (9)	3 9 (6)	-4 7 (11)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.9482
	Mean (Std)	69.71 (8.08)	69.06 (7.26)	6 (8.31)	6.18 (6.57)	-0.18 (11.03)	Signed Rank	0.8077
	Median (min;max)	68 (59;86)	67 (58;92)	7 (-12;22)	6 (-6;18)	-1 (-30;14)		
	Q1, Q3 (IQR)	64 73 (9)	66 71 (5)	0 10 (10)	3 11 (8)	-6 6 (12)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.7638
	Mean (Std)	70.35 (9.47)	70.35 (6.69)	6.65 (8.69)	7.47 (6.35)	-0.82 (11.11)	Signed Rank	0.7916
	Median (min;max)	67 (59;87)	71 (62;87)	8 (-12;16)	8 (-6;21)	3 (-25;17)		
	Q1, Q3 (IQR)	63 77 (14)	65 72 (7)	4 13 (9)	5 10 (5)	-7 6 (13)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-203 Change in pulse rate (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg (alt. manu. proc.)

Time point (min)	Statistics	PSWL	ZSA3	Change in PSWL	Change in ZSA3	Change in PSWL - Change in ZSA3	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	63.71 (10.82)	63.29 (6.92)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	61 (51;98)	63 (52;77)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	59 67 (8)	58 68 (10)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.7306
	Mean (Std)	64.71 (5.71)	63.53 (6.26)	1 (6.38)	0.24 (5.95)	0.76 (9)	Signed Rank	0.3820
	Median (min;max)	64 (58;78)	64 (52;76)	1 (-20;9)	0 (-13;9)	2 (-25;14)		
	Q1, Q3 (IQR)	60 69 (9)	60 68 (8)	0 4 (4)	-3 5 (8)	-3 7 (10)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0972
	Mean (Std)	69 (9.95)	64.18 (6.59)	5.29 (8.99)	0.88 (4.46)	4.41 (10.33)	Signed Rank	0.0624
	Median (min;max)	66 (54;87)	67 (53;76)	3 (-17;19)	1 (-10;7)	4 (-23;20)		
	Q1, Q3 (IQR)	62 79 (17)	60 68 (8)	1 13 (12)	-2 5 (7)	0 12 (12)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3845
	Mean (Std)	70.06 (9.34)	66.94 (9.84)	6.35 (8.84)	3.65 (7.75)	2.71 (12.48)	Signed Rank	0.2681
	Median (min;max)	68 (55;87)	66 (53;86)	6 (-11;20)	4 (-16;17)	3 (-25;20)		
	Q1, Q3 (IQR)	66 73 (7)	60 71 (11)	2 11 (9)	0 8 (8)	-3 12 (15)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6438
	Mean (Std)	69.71 (8.08)	68 (10.02)	6 (8.31)	4.71 (7.99)	1.29 (11.32)	Signed Rank	0.2995
	Median (min;max)	68 (59;86)	67 (52;89)	7 (-12;22)	4 (-11;20)	5 (-28;14)		
	Q1, Q3 (IQR)	64 73 (9)	61 69 (8)	0 10 (10)	0 6 (6)	-4 8 (12)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3556
	Mean (Std)	70.35 (9.47)	67.47 (8.89)	6.65 (8.69)	4.18 (7.66)	2.47 (10.71)	Signed Rank	0.2014
	Median (min;max)	67 (59;87)	66 (55;86)	8 (-12;16)	5 (-10;17)	4 (-26;15)		
	Q1, Q3 (IQR)	63 77 (14)	60 73 (13)	4 13 (9)	-3 9 (12)	-3 9 (12)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-204 Change in pulse rate (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg

Time point (min)	Statistics	PSWL	ZS6	Change in PSWL	Change in ZS6	Change in PSWL - Change in ZS6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	63.71 (10.82)	64 (9.12)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	61 (51;98)	63 (48;87)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	59 67 (8)	59 68 (9)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.5438
	Mean (Std)	64.71 (5.71)	66.35 (8.57)	1 (6.38)	2.35 (4.94)	-1.35 (8.99)	Signed Rank	0.9360
	Median (min;max)	64 (58;78)	67 (48;86)	1 (-20;9)	1 (-4;16)	1 (-25;10)		
	Q1, Q3 (IQR)	60 69 (9)	61 70 (9)	0 4 (4)	-1 5 (6)	-5 4 (9)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.8348
	Mean (Std)	69 (9.95)	69.82 (8.46)	5.29 (8.99)	5.82 (7.48)	-0.53 (10.3)	Signed Rank	0.7733
	Median (min;max)	66 (54;87)	67 (55;87)	3 (-17;19)	4 (-10;19)	-1 (-18;19)		
	Q1, Q3 (IQR)	62 79 (17)	63 76 (13)	1 13 (12)	1 10 (9)	-6 4 (10)		

Time point (min)	Statistics	PSWL	ZS6	Change in PSWL	Change in ZS6	Change in PSWL - Change in ZS6	Statistical test	P-value
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2917
	Mean (Std)	70.06 (9.34)	73.53 (8.7)	6.35 (8.84)	9.53 (8.9)	-3.18 (12.01)	Signed Rank	0.4102
	Median (min;max)	68 (55;87)	70 (61;91)	6 (-11;20)	11 (-5;23)	-1 (-31;13)		
	Q1, Q3 (IQR)	66 73 (7)	68 80 (12)	2 11 (9)	2 17 (15)	-10 6 (16)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1816
	Mean (Std)	69.71 (8.08)	73.88 (6.89)	6 (8.31)	9.88 (9.68)	-3.88 (11.46)	Signed Rank	0.2799
	Median (min;max)	68 (59;86)	76 (60;87)	7 (-12;22)	13 (-9;25)	-3 (-28;16)		
	Q1, Q3 (IQR)	64 73 (9)	68 78 (10)	0 10 (10)	2 16 (14)	-7 2 (9)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2795
	Mean (Std)	70.35 (9.47)	73.24 (9.93)	6.65 (8.69)	9.24 (9.28)	-2.59 (9.53)	Signed Rank	0.2258
	Median (min;max)	67 (59;87)	72 (59;89)	8 (-12;16)	10 (-9;26)	-2 (-22;20)		
	Q1, Q3 (IQR)	63 77 (14)	66 81 (15)	4 13 (9)	2 15 (13)	-9 1 (10)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-205 Change in pulse rate (beats/min): Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	PSWL	ZSA6	Change in PSWL	Change in ZSA6	Change in PSWL - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	63.71 (10.82)	64.06 (11.17)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	61 (51;98)	63 (51;99)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	59 67 (8)	57 67 (10)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.6886
	Mean (Std)	64.71 (5.71)	63 (6.07)	1 (6.38)	-0.88 (10.58)	1.44 (14.07)	Signed Rank	0.9449
	Median (min;max)	64 (58;78)	63 (48;71)	1 (-20;9)	1 (-37;9)	0.5 (-22;44)		
	Q1, Q3 (IQR)	60 69 (9)	60 67.5 (7.5)	0 4 (4)	-2 4.5 (6.5)	-6.5 3 (9.5)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.5542
	Mean (Std)	69 (9.95)	72 (12.29)	5.29 (8.99)	7.94 (14.15)	-2.65 (18.07)	Signed Rank	0.1775
	Median (min;max)	66 (54;87)	72 (54;103)	3 (-17;19)	9 (-33;36)	-6 (-33;48)		
	Q1, Q3 (IQR)	62 79 (17)	65 75 (10)	1 13 (12)	5 12 (7)	-12 2 (14)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.7418
	Mean (Std)	70.06 (9.34)	71.71 (10.37)	6.35 (8.84)	7.65 (12.2)	-1.29 (15.92)	Signed Rank	0.4235
	Median (min;max)	68 (55;87)	69 (55;90)	6 (-11;20)	8 (-30;23)	-3 (-32;45)		
	Q1, Q3 (IQR)	66 73 (7)	64 79 (15)	2 11 (9)	4 17 (13)	-7 3 (10)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.8017
	Mean (Std)	69.71 (8.08)	71 (8.89)	6 (8.31)	6.94 (11.33)	-0.94 (15.2)	Signed Rank	0.5240
	Median (min;max)	68 (59;86)	71 (55;88)	7 (-12;22)	9 (-28;22)	-2 (-30;43)		
	Q1, Q3 (IQR)	64 73 (9)	68 73 (5)	0 10 (10)	3 13 (10)	-9 4 (13)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.9410
	Mean (Std)	70.35 (9.47)	71 (7.95)	6.65 (8.69)	6.94 (11.85)	-0.29 (16.12)	Signed Rank	0.8905
	Median (min;max)	67 (59;87)	70 (61;90)	8 (-12;16)	10 (-29;23)	1 (-29;44)		
	Q1, Q3 (IQR)	63 77 (14)	66 76 (10)	4 13 (9)	4 12 (8)	-12 5 (17)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-206 Change in pulse rate (beats/min): ZYN® Smooth 3 mg vs. ZYN® Smooth 3 mg (alt. manu. proc.)

Time point (min)	Statistics	ZS3	ZSA3	Change in ZS3	Change in ZSA3	Change in ZS3 - Change in ZSA3	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	62.88 (7.18)	63.29 (6.92)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	62 (50;74)	63 (52;77)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	58 70 (12)	58 68 (10)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1654
	Mean (Std)	65.94 (7.44)	63.53 (6.26)	3.06 (6.3)	0.24 (5.95)	2.82 (8.01)	Signed Rank	0.1624
	Median (min;max)	65 (54;82)	64 (52;76)	2 (-7;19)	0 (-13;9)	3 (-16;17)		
	Q1, Q3 (IQR)	61 71 (10)	60 68 (8)	-1 6 (7)	-3 5 (8)	-2 9 (11)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0960
	Mean (Std)	67.06 (6.76)	64.18 (6.59)	4.18 (6.04)	0.88 (4.46)	3.29 (7.68)	Signed Rank	0.0529
	Median (min;max)	65 (56;81)	67 (53;76)	5 (-13;14)	1 (-10;7)	2 (-18;13)		
	Q1, Q3 (IQR)	63 72 (9)	60 68 (8)	2 7 (5)	-2 5 (7)	0 9 (9)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2139
	Mean (Std)	68.94 (6.81)	66.94 (9.84)	6.06 (6.08)	3.65 (7.75)	2.41 (7.68)	Signed Rank	0.2360
	Median (min;max)	68 (60;81)	66 (53;86)	5 (-8;21)	4 (-16;17)	3 (-9;18)		
	Q1, Q3 (IQR)	63 74 (11)	60 71 (11)	3 9 (6)	0 8 (8)	-3 8 (11)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.4860
	Mean (Std)	69.06 (7.26)	68 (10.02)	6.18 (6.57)	4.71 (7.99)	1.47 (8.5)	Signed Rank	0.4865
	Median (min;max)	67 (58;92)	67 (52;89)	6 (-6;18)	4 (-11;20)	2 (-17;19)		
	Q1, Q3 (IQR)	66 71 (5)	61 69 (8)	3 11 (8)	0 6 (6)	-4 5 (9)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1876
	Mean (Std)	70.35 (6.69)	67.47 (8.89)	7.47 (6.35)	4.18 (7.66)	3.29 (9.87)	Signed Rank	0.1487
	Median (min;max)	71 (62;87)	66 (55;86)	8 (-6;21)	5 (-10;17)	4 (-18;19)		
	Q1, Q3 (IQR)	65 72 (7)	60 73 (13)	5 10 (5)	-3 9 (12)	-1 11 (12)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-207 Change in pulse rate (beats/min): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg

Time point (min)	Statistics	ZS3	ZS6	Change in ZS3	Change in ZS6	Change in ZS3 - Change in ZS6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	62.88 (7.18)	64 (9.12)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	62 (50;74)	63 (48;87)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	58 70 (12)	59 68 (9)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.7356
	Mean (Std)	65.94 (7.44)	66.35 (8.57)	3.06 (6.3)	2.35 (4.94)	0.71 (8.47)	Signed Rank	0.6963
	Median (min;max)	65 (54;82)	67 (48;86)	2 (-7;19)	1 (-4;16)	0 (-17;18)		
	Q1, Q3 (IQR)	61 71 (10)	61 70 (9)	-1 6 (7)	-1 5 (6)	-2 5 (7)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.4488
	Mean (Std)	67.06 (6.76)	69.82 (8.46)	4.18 (6.04)	5.82 (7.48)	-1.65 (8.75)	Signed Rank	0.3564
	Median (min;max)	65 (56;81)	67 (55;87)	5 (-13;14)	4 (-10;19)	-2 (-17;17)		

Time point (min)	Statistics	ZS3	ZS6	Change in ZS3	Change in ZS6	Change in ZS3 - Change in ZS6	Statistical test	P-value
	Q1, Q3 (IQR)	63 72 (9)	63 76 (13)	2 7 (5)	1 10 (9)	-6 3 (9)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2097
	Mean (Std)	68.94 (6.81)	73.53 (8.7)	6.06 (6.08)	9.53 (8.9)	-3.47 (10.95)	Signed Rank	0.2158
	Median (min;max)	68 (60;81)	70 (61;91)	5 (-8;21)	11 (-5;23)	-4 (-21;15)		
	Q1, Q3 (IQR)	63 74 (11)	68 80 (12)	3 9 (6)	2 17 (15)	-13 5 (18)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1311
	Mean (Std)	69.06 (7.26)	73.88 (6.89)	6.18 (6.57)	9.88 (9.68)	-3.71 (9.6)	Signed Rank	0.1623
	Median (min;max)	67 (58;92)	76 (60;87)	6 (-6;18)	13 (-9;25)	-4 (-23;12)		
	Q1, Q3 (IQR)	66 71 (5)	68 78 (10)	3 11 (8)	2 16 (14)	-7 2 (9)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3569
	Mean (Std)	70.35 (6.69)	73.24 (9.93)	7.47 (6.35)	9.24 (9.28)	-1.76 (7.67)	Signed Rank	0.5321
	Median (min;max)	71 (62;87)	72 (59;89)	8 (-6;21)	10 (-9;26)	-1 (-16;8)		
	Q1, Q3 (IQR)	65 72 (7)	66 81 (15)	5 10 (5)	2 15 (13)	-5 3 (8)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by:
Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-208 Change in pulse rate (beats/min): ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	ZS3	ZSA6	Change in ZS3	Change in ZSA6	Change in ZS3 - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	62.88 (7.18)	64.06 (11.17)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	62 (50;74)	63 (51;99)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	58 70 (12)	57 67 (10)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.2009
	Mean (Std)	65.94 (7.44)	63 (6.07)	3.06 (6.3)	-0.88 (10.58)	4 (11.96)	Signed Rank	0.3404
	Median (min;max)	65 (54;82)	63 (48;71)	2 (-7;19)	1 (-37;9)	1 (-11;36)		
	Q1, Q3 (IQR)	61 71 (10)	60 67.5 (7.5)	-1 6 (7)	-2 4.5 (6.5)	-2.5 6.5 (9)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3123
	Mean (Std)	67.06 (6.76)	72 (12.29)	4.18 (6.04)	7.94 (14.15)	-3.76 (14.88)	Signed Rank	0.1122
	Median (min;max)	65 (56;81)	72 (54;103)	5 (-13;14)	9 (-33;36)	-5 (-36;34)		
	Q1, Q3 (IQR)	63 72 (9)	65 75 (10)	2 7 (5)	5 12 (7)	-10 -2 (8)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6231
	Mean (Std)	68.94 (6.81)	71.71 (10.37)	6.06 (6.08)	7.65 (12.2)	-1.59 (13.07)	Signed Rank	0.3285
	Median (min;max)	68 (60;81)	69 (55;90)	5 (-8;21)	8 (-30;23)	-4 (-20;34)		
	Q1, Q3 (IQR)	63 74 (11)	64 79 (15)	3 9 (6)	4 17 (13)	-9 5 (14)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.8083
	Mean (Std)	69.06 (7.26)	71 (8.89)	6.18 (6.57)	6.94 (11.33)	-0.76 (12.78)	Signed Rank	0.4696
	Median (min;max)	67 (58;92)	71 (55;88)	6 (-6;18)	9 (-28;22)	-3 (-26;37)		
	Q1, Q3 (IQR)	66 71 (5)	68 73 (5)	3 11 (8)	3 13 (10)	-7 3 (10)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.8613
	Mean (Std)	70.35 (6.69)	71 (7.95)	7.47 (6.35)	6.94 (11.85)	0.53 (12.29)	Signed Rank	0.6230
	Median (min;max)	71 (62;87)	70 (61;90)	8 (-6;21)	10 (-29;23)	-1 (-16;38)		
	Q1, Q3 (IQR)	65 72 (7)	66 76 (10)	5 10 (5)	4 12 (8)	-4 3 (7)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-209 Change in pulse rate (beats/min): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg

Time point (min)	Statistics	ZSA3	ZS6	Change in ZSA3	Change in ZS6	Change in ZSA3 - Change in ZS6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	63.29 (6.92)	64 (9.12)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	63 (52;77)	63 (48;87)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	58 68 (10)	59 68 (9)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3435
	Mean (Std)	63.53 (6.26)	66.35 (8.57)	0.24 (5.95)	2.35 (4.94)	-2.12 (8.94)	Signed Rank	0.4615
	Median (min;max)	64 (52;76)	67 (48;86)	0 (-13;9)	1 (-4;16)	0 (-19;10)		
	Q1, Q3 (IQR)	60 68 (8)	61 70 (9)	-3 5 (8)	-1 5 (6)	-9 6 (15)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0367
	Mean (Std)	64.18 (6.59)	69.82 (8.46)	0.88 (4.46)	5.82 (7.48)	-4.94 (8.94)	Signed Rank	0.0611
	Median (min;max)	67 (53;76)	67 (55;87)	1 (-10;7)	4 (-10;19)	-5 (-20;7)		
	Q1, Q3 (IQR)	60 68 (8)	63 76 (13)	-2 5 (7)	1 10 (9)	-12 1 (13)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0754
	Mean (Std)	66.94 (9.84)	73.53 (8.7)	3.65 (7.75)	9.53 (8.9)	-5.88 (12.76)	Signed Rank	0.0653
	Median (min;max)	66 (53;86)	70 (61;91)	4 (-16;17)	11 (-5;23)	-5 (-39;16)		
	Q1, Q3 (IQR)	60 71 (11)	68 80 (12)	0 8 (8)	2 17 (15)	-12 1 (13)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0507
	Mean (Std)	68 (10.02)	73.88 (6.89)	4.71 (7.99)	9.88 (9.68)	-5.18 (10.1)	Signed Rank	0.0422
	Median (min;max)	67 (52;89)	76 (60;87)	4 (-11;20)	13 (-9;25)	-6 (-19;16)		
	Q1, Q3 (IQR)	61 69 (8)	68 78 (10)	0 6 (6)	2 16 (14)	-13 0 (13)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0281
	Mean (Std)	67.47 (8.89)	73.24 (9.93)	4.18 (7.66)	9.24 (9.28)	-5.06 (8.64)	Signed Rank	0.0147
	Median (min;max)	66 (55;86)	72 (59;89)	5 (-10;17)	10 (-9;26)	-5 (-22;16)		
	Q1, Q3 (IQR)	60 73 (13)	66 81 (15)	-3 9 (12)	2 15 (13)	-9 0 (9)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-210 Change in pulse rate (beats/min): ZYN[®] Smooth 3 mg (alt. manu. proc.) vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	ZSA3	ZSA6	Change in ZSA3	Change in ZSA6	Change in ZSA3 - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	63.29 (6.92)	64.06 (11.17)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	63 (52;77)	63 (51;99)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	58 68 (10)	57 67 (10)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.7060
	Mean (Std)	63.53 (6.26)	63 (6.07)	0.24 (5.95)	-0.88 (10.58)	1.06 (11.05)	Signed Rank	0.9902
	Median (min;max)	64 (52;76)	63 (48;71)	0 (-13;9)	1 (-37;9)	0.5 (-14;32)		
	Q1, Q3 (IQR)	60 68 (8)	60 67.5 (7.5)	-3 5 (8)	-2 4.5 (6.5)	-6.5 6.5 (13)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0851

Time point (min)	Statistics	ZSA3	ZSA6	Change in ZSA3	Change in ZSA6	Change in ZSA3 - Change in ZSA6	Statistical test	P-value
	Mean (Std)	64.18 (6.59)	72 (12.29)	0.88 (4.46)	7.94 (14.15)	-7.06 (15.86)	Signed Rank	0.0315
	Median (min;max)	67 (53;76)	72 (54;103)	1 (-10;7)	9 (-33;36)	-4 (-38;35)		
	Q1, Q3 (IQR)	60 68 (8)	65 75 (10)	-2 5 (7)	5 12 (7)	-16 -1 (15)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2383
	Mean (Std)	66.94 (9.84)	71.71 (10.37)	3.65 (7.75)	7.65 (12.2)	-4 (13.46)	Signed Rank	0.1732
	Median (min;max)	66 (53;86)	69 (55;90)	4 (-16;17)	8 (-30;23)	-4 (-23;31)		
	Q1, Q3 (IQR)	60 71 (11)	64 79 (15)	0 8 (8)	4 17 (13)	-14 0 (14)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.4110
	Mean (Std)	68 (10.02)	71 (8.89)	4.71 (7.99)	6.94 (11.33)	-2.24 (10.92)	Signed Rank	0.1554
	Median (min;max)	67 (52;89)	71 (55;88)	4 (-11;20)	9 (-28;22)	-4 (-17;30)		
	Q1, Q3 (IQR)	61 69 (8)	68 73 (5)	0 6 (6)	3 13 (10)	-8 2 (10)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3375
	Mean (Std)	67.47 (8.89)	71 (7.95)	4.18 (7.66)	6.94 (11.85)	-2.76 (11.53)	Signed Rank	0.1395
	Median (min;max)	66 (55;86)	70 (61;90)	5 (-10;17)	10 (-29;23)	-3 (-27;29)		
	Q1, Q3 (IQR)	60 73 (13)	66 76 (10)	-3 9 (12)	4 12 (8)	-8 1 (9)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-211 Change in pulse rate (beats/min): ZYN[®] Smooth 6 mg vs. ZYN[®] Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	ZS6	ZSA6	Change in ZS6	Change in ZSA6	Change in ZS6 - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	
	Mean (Std)	64 (9.12)	64.06 (11.17)	0 (0)	0 (0)	0 (0)	Signed Rank	
	Median (min;max)	63 (48;87)	63 (51;99)	0 (0;0)	0 (0;0)	0 (0;0)		
	Q1, Q3 (IQR)	59 68 (9)	57 67 (10)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.2696
	Mean (Std)	66.35 (8.57)	63 (6.07)	2.35 (4.94)	-0.88 (10.58)	3.13 (10.9)	Signed Rank	0.4247
	Median (min;max)	67 (48;86)	63 (48;71)	1 (-4;16)	1 (-37;9)	2 (-11;36)		
	Q1, Q3 (IQR)	61 70 (9)	60 67.5 (7.5)	-1 5 (6)	-2 4.5 (6.5)	-3 8 (11)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.5389
	Mean (Std)	69.82 (8.46)	72 (12.29)	5.82 (7.48)	7.94 (14.15)	-2.12 (13.91)	Signed Rank	0.3223
	Median (min;max)	67 (55;87)	72 (54;103)	4 (-10;19)	9 (-33;36)	-5 (-26;34)		
	Q1, Q3 (IQR)	63 76 (13)	65 75 (10)	1 10 (9)	5 12 (7)	-9 5 (14)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.5455
	Mean (Std)	73.53 (8.7)	71.71 (10.37)	9.53 (8.9)	7.65 (12.2)	1.88 (12.56)	Signed Rank	0.6856
	Median (min;max)	70 (61;91)	69 (55;90)	11 (-5;23)	8 (-30;23)	-1 (-25;32)		
	Q1, Q3 (IQR)	68 80 (12)	64 79 (15)	2 17 (15)	4 17 (13)	-5 8 (13)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.3506
	Mean (Std)	73.88 (6.89)	71 (8.89)	9.88 (9.68)	6.94 (11.33)	2.94 (12.61)	Signed Rank	0.4651

Time point (min)	Statistics	ZS6	ZSA6	Change in ZS6	Change in ZSA6	Change in ZS6 - Change in ZSA6	Statistical test	P-value
60	Median (min;max)	76 (60;87)	71 (55;88)	13 (-9;25)	9 (-28;22)	1 (-18;41)		
	Q1, Q3 (IQR)	68 78 (10)	68 73 (5)	2 16 (14)	3 13 (10)	-4 7 (11)		
	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.5395
	Mean (Std)	73.24 (9.93)	71 (7.95)	9.24 (9.28)	6.94 (11.85)	2.29 (15.09)	Signed Rank	0.6684
	Median (min;max)	72 (59;89)	70 (61;90)	10 (-9;26)	10 (-29;23)	3 (-23;43)		
	Q1, Q3 (IQR)	66 81 (15)	66 76 (10)	2 15 (13)	4 12 (8)	-7 9 (16)		

SM17_03 Analysis of secondary endpoint - Pulse, SAS program: sec_endpoint_pulse.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-212 Pulse rate by treatment

Assessment (Unit)	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
Pulse Rate (beats/min)	Measured value	ZYN® Smooth 3 mg	Timepoint 0:00	17	50	74	62.9	62	7.18
			Timepoint 0:05	17	54	82	65.9	65	7.44
			Timepoint 0:10	17	56	81	67.1	65	6.76
			Timepoint 0:15	17	60	81	68.9	68	6.81
			Timepoint 0:30	17	58	92	69.1	67	7.26
			Timepoint 1:00	17	62	87	70.4	71	6.69
		ZYN® Smooth 6 mg	Timepoint 0:00	17	48	87	64	63	9.12
			Timepoint 0:05	17	48	86	66.4	67	8.57
			Timepoint 0:10	17	55	87	69.8	67	8.46
			Timepoint 0:15	17	61	91	73.5	70	8.7
			Timepoint 0:30	17	60	87	73.9	76	6.89
			Timepoint 1:00	17	59	89	73.2	72	9.93
		ZYN® Smooth 3 mg (alt. manu. proc.)	Timepoint 0:00	17	52	77	63.3	63	6.92
			Timepoint 0:05	17	52	76	63.5	64	6.26
			Timepoint 0:10	17	53	76	64.2	67	6.59
			Timepoint 0:15	17	53	86	66.9	66	9.84
			Timepoint 0:30	17	52	89	68	67	10
			Timepoint 1:00	17	55	86	67.5	66	8.89
		ZYN® Smooth 6 mg (alt. manu. proc.)	Timepoint 0:00	17	51	99	64.1	63	11.2
			Timepoint 0:05	16	48	71	63	63	6.07
			Timepoint 0:10	17	54	103	72	72	12.3
			Timepoint 0:15	17	55	90	71.7	69	10.4
			Timepoint 0:30	17	55	88	71	71	8.89
			Timepoint 1:00	17	61	90	71	70	7.95
		Swedish portion snus PSWL 1.0 g (8 mg)	Timepoint 0:00	17	51	98	63.7	61	10.8

Assessment (Unit)	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
Absolute change from pre-dose baseline	ZYN® Smooth 3 mg		Timepoint 0:05	17	58	78	64.7	64	5.71
			Timepoint 0:10	17	54	87	69	66	9.95
			Timepoint 0:15	17	55	87	70.1	68	9.34
			Timepoint 0:30	17	59	86	69.7	68	8.08
			Timepoint 1:00	17	59	87	70.4	67	9.47
			Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	-7	19	3.06	2	6.3
			Timepoint 0:10	17	-13	14	4.18	5	6.04
			Timepoint 0:15	17	-8	21	6.06	5	6.08
			Timepoint 0:30	17	-6	18	6.18	6	6.57
			Timepoint 1:00	17	-6	21	7.47	8	6.35
			Timepoint 0:00	17	0	0	0	0	0
	ZYN® Smooth 6 mg		Timepoint 0:05	17	-4	16	2.35	1	4.94
			Timepoint 0:10	17	-10	19	5.82	4	7.48
			Timepoint 0:15	17	-5	23	9.53	11	8.9
			Timepoint 0:30	17	-9	25	9.88	13	9.68
			Timepoint 1:00	17	-9	26	9.24	10	9.28
			Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	-13	9	0.235	0	5.95
			Timepoint 0:10	17	-10	7	0.882	1	4.46
			Timepoint 0:15	17	-16	17	3.65	4	7.75
			Timepoint 0:30	17	-11	20	4.71	4	7.99
			Timepoint 1:00	17	-10	17	4.18	5	7.66
			Timepoint 0:00	17	0	0	0	0	0
	ZYN® Smooth 3 mg (alt. manu. proc.)		Timepoint 0:05	16	-37	9	-0.875	1	10.6
			Timepoint 0:10	17	-33	36	7.94	9	14.1
			Timepoint 0:15	17	-30	23	7.65	8	12.2
			Timepoint 0:30	17	-30	23	7.65	8	12.2

Assessment (Unit)	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
Relative change from pre-dose baseline (%)	Swedish portion snus PSWL 1.0 g (8 mg)		Timepoint 0:30	17	-28	22	6.94	9	11.3
			Timepoint 1:00	17	-29	23	6.94	10	11.9
			Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	-20	9	1	1	6.38
			Timepoint 0:10	17	-17	19	5.29	3	8.99
			Timepoint 0:15	17	-11	20	6.35	6	8.84
			Timepoint 0:30	17	-12	22	6	7	8.31
			Timepoint 1:00	17	-12	16	6.65	8	8.69
		ZYN® Smooth 3 mg	Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	-10	36	5.41	3	11.2
			Timepoint 0:10	17	-18	26	7.41	8	9.89
			Timepoint 0:15	17	-11	40	10.2	8	10.9
			Timepoint 0:30	17	-8	32	10.6	9	11.1
			Timepoint 1:00	17	-8	34	12.6	14	10.4
	ZYN® Smooth 6 mg		Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	-5	31	4.06	2	8.65
			Timepoint 0:10	17	-14	29	10	7	12
			Timepoint 0:15	17	-7	37	16	19	14.7
			Timepoint 0:30	17	-10	46	17.2	20	16.8
			Timepoint 1:00	17	-13	54	15.6	15	16.7
		ZYN® Smooth 3 mg (alt. manu. proc.)	Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	-17	17	0.941	0	9.36
			Timepoint 0:10	17	-13	10	1.82	2	6.71
			Timepoint 0:15	17	-21	25	6	6	11.2
			Timepoint 0:30	17	-14	32	7.59	6	11.9
			Timepoint 1:00	17	-13	25	7	10	11.5
		ZYN® Smooth 6 mg (alt. manu. proc.)	Timepoint 0:00	17	0	0	0	0	0

Assessment (Unit)	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		Swedish portion snus PSWL 1.0 g (8 mg)	Timepoint 0:05	16	-37	16	0.375	2	12.5
			Timepoint 0:10	17	-33	54	13.9	16	18.5
			Timepoint 0:15	17	-30	34	13.4	14	15.8
			Timepoint 0:30	17	-28	33	12.5	16	14.8
			Timepoint 1:00	17	-29	34	12.8	16	15.8
			Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	-20	17	2.82	2	8.71
			Timepoint 0:10	17	-17	31	9.41	4	13.2
			Timepoint 0:15	17	-11	39	11.2	12	14.4
			Timepoint 0:30	17	-12	36	10.8	11	13.5
			Timepoint 1:00	17	-12	29	11.6	11	13.3

Data based on PPS population

SM17_03 VS tabulations, SAS program: safety_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:57:33

14.3.2.10 Visual Analogue Scale

Table 14.3-213 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg

Time point (min)	Statistics	PSWL	ZS3	Change in PSWL	Change in ZS3	Change in PSWL - Change in ZS3	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.9181
	Mean (Std)	12.65 (16.11)	11.94 (25.19)	12.65 (16.11)	11.94 (25.19)	0.71 (27.86)	Signed Rank	0.4819
	Median (min;max)	9 (0;56)	0 (0;90)	9 (0;56)	0 (0;90)	0 (-75;56)		
	Q1, Q3 (IQR)	0 15 (15)	0 6 (6)	0 15 (15)	0 6 (6)	0 7 (7)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.4359
	Mean (Std)	17.76 (15.28)	12.53 (22.66)	17.76 (15.28)	12.53 (22.66)	5.24 (27.01)	Signed Rank	0.1316
	Median (min;max)	17 (0;60)	3 (0;70)	17 (0;60)	3 (0;70)	3 (-53;60)		
	Q1, Q3 (IQR)	4 21 (17)	0 14 (14)	4 21 (17)	0 14 (14)	0 18 (18)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0140
	Mean (Std)	21.06 (18.22)	6.94 (9.24)	21.06 (18.22)	6.94 (9.24)	14.12 (21.1)	Signed Rank	0.0129
	Median (min;max)	24 (0;56)	4 (0;31)	24 (0;56)	4 (0;31)	12 (-31;47)		
	Q1, Q3 (IQR)	6 37 (31)	0 11 (11)	6 37 (31)	0 11 (11)	0 35 (35)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0024
	Mean (Std)	18.82 (18)	4.65 (5.54)	18.82 (18)	4.65 (5.54)	14.18 (16.2)	Signed Rank	0.0009
	Median (min;max)	14 (0;62)	3 (0;18)	14 (0;62)	3 (0;18)	12 (-6;55)		
	Q1, Q3 (IQR)	6 25 (19)	0 7 (7)	6 25 (19)	0 7 (7)	0 22 (22)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0377
	Mean (Std)	12.71 (15.08)	5.71 (9.73)	12.71 (15.08)	5.71 (9.73)	7 (12.74)	Signed Rank	0.0303
	Median (min;max)	10 (0;50)	2 (0;39)	10 (0;50)	2 (0;39)	3 (-9;42)		
	Q1, Q3 (IQR)	0 15 (15)	0 6 (6)	0 15 (15)	0 6 (6)	0 9 (9)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-214 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 3 mg (alt. manu. proc.)

Time point (min)	Statistics	PSWL	ZSA3	Change in PSWL	Change in ZSA3	Change in PSWL - Change in ZSA3	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0206
	Mean (Std)	12.65 (16.11)	2.41 (4.32)	12.65 (16.11)	2.41 (4.32)	10.24 (16.43)	Signed Rank	0.0020
	Median (min;max)	9 (0;56)	1 (0;16)	9 (0;56)	1 (0;16)	5 (-1;56)		
	Q1, Q3 (IQR)	0 15 (15)	0 3 (3)	0 15 (15)	0 3 (3)	0 9 (9)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0128
	Mean (Std)	17.76 (15.28)	5.88 (7.38)	17.76 (15.28)	5.88 (7.38)	11.88 (17.48)	Signed Rank	0.0083

Time point (min)	Statistics	PSWL	ZSA3	Change in PSWL	Change in ZSA3	Change in PSWL - Change in ZSA3	Statistical test	P-value
	Median (min;max)	17 (0;60)	4 (0;28)	17 (0;60)	4 (0;28)	7 (-11;60)		
	Q1, Q3 (IQR)	4 21 (17)	0 9 (9)	4 21 (17)	0 9 (9)	0 18 (18)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0027
	Mean (Std)	21.06 (18.22)	7.88 (7.93)	21.06 (18.22)	7.88 (7.93)	13.18 (15.36)	Signed Rank	0.0050
	Median (min;max)	24 (0;56)	6 (0;32)	24 (0;56)	6 (0;32)	13 (-7;36)		
	Q1, Q3 (IQR)	6 37 (31)	2 11 (9)	6 37 (31)	2 11 (9)	0 26 (26)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0215
	Mean (Std)	18.82 (18)	8 (8.4)	18.82 (18)	8 (8.4)	10.82 (17.52)	Signed Rank	0.0134
	Median (min;max)	14 (0;62)	6 (0;26)	14 (0;62)	6 (0;26)	7 (-23;55)		
	Q1, Q3 (IQR)	6 25 (19)	0 15 (15)	6 25 (19)	0 15 (15)	0 18 (18)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0272
	Mean (Std)	12.71 (15.08)	6.65 (8.06)	12.71 (15.08)	6.65 (8.06)	6.06 (10.27)	Signed Rank	0.0117
	Median (min;max)	10 (0;50)	4 (0;25)	10 (0;50)	4 (0;25)	0 (-3;33)		
	Q1, Q3 (IQR)	0 15 (15)	0 9 (9)	0 15 (15)	0 9 (9)	0 7 (7)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-215 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg

Time point (min)	Statistics	PSWL	ZS6	Change in PSWL	Change in ZS6	Change in PSWL - Change in ZS6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0572
	Mean (Std)	12.65 (16.11)	4.06 (5.85)	12.65 (16.11)	4.06 (5.85)	8.59 (17.28)	Signed Rank	0.0417
	Median (min;max)	9 (0;56)	1 (0;21)	9 (0;56)	1 (0;21)	3 (-8;56)		
	Q1, Q3 (IQR)	0 15 (15)	0 7 (7)	0 15 (15)	0 7 (7)	0 11 (11)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0541
	Mean (Std)	17.76 (15.28)	10 (10.81)	17.76 (15.28)	10 (10.81)	7.76 (15.41)	Signed Rank	0.0571
	Median (min;max)	17 (0;60)	7 (0;38)	17 (0;60)	7 (0;38)	4 (-13;48)		
	Q1, Q3 (IQR)	4 21 (17)	1 14 (13)	4 21 (17)	1 14 (13)	0 15 (15)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0087
	Mean (Std)	21.06 (18.22)	11.35 (12.04)	21.06 (18.22)	11.35 (12.04)	9.71 (13.39)	Signed Rank	0.0085
	Median (min;max)	24 (0;56)	8 (0;39)	24 (0;56)	8 (0;39)	3 (-4;38)		
	Q1, Q3 (IQR)	6 37 (31)	2 13 (11)	6 37 (31)	2 13 (11)	0 17 (17)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0094
	Mean (Std)	18.82 (18)	7.94 (7.72)	18.82 (18)	7.94 (7.72)	10.88 (15.2)	Signed Rank	0.0007
	Median (min;max)	14 (0;62)	7 (0;26)	14 (0;62)	7 (0;26)	5 (-1;58)		
	Q1, Q3 (IQR)	6 25 (19)	0 12 (12)	6 25 (19)	0 12 (12)	0 15 (15)		

Time point (min)	Statistics	PSWL	ZS6	Change in PSWL	Change in ZS6	Change in PSWL - Change in ZS6	Statistical test	P-value
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0625
	Mean (Std)	12.71 (15.08)	6.06 (6.21)	12.71 (15.08)	6.06 (6.21)	6.65 (13.69)	Signed Rank	0.0811
	Median (min;max)	10 (0;50)	4 (0;22)	10 (0;50)	4 (0;22)	0 (-5;46)		
	Q1, Q3 (IQR)	0 15 (15)	0 10 (10)	0 15 (15)	0 10 (10)	0 8 (8)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-216 Change in VAS: Swedish portion snus PSWL 1.0 g (8 mg) vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	PSWL	ZSA6	Change in PSWL	Change in ZSA6	Change in PSWL - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.3974
	Mean (Std)	12.65 (16.11)	8.25 (13.43)	12.65 (16.11)	8.25 (13.43)	4.44 (20.38)	Signed Rank	0.3667
	Median (min;max)	9 (0;56)	0 (0;44)	9 (0;56)	0 (0;44)	0.5 (-35;56)		
	Q1, Q3 (IQR)	0 15 (15)	0 12.5 (12.5)	0 15 (15)	0 12.5 (12.5)	-1 10.5 (11.5)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0933
	Mean (Std)	17.76 (15.28)	9.82 (12.65)	17.76 (15.28)	9.82 (12.65)	7.94 (18.35)	Signed Rank	0.0938
	Median (min;max)	17 (0;60)	7 (0;46)	17 (0;60)	7 (0;46)	5 (-29;52)		
	Q1, Q3 (IQR)	4 21 (17)	0 10 (10)	4 21 (17)	0 10 (10)	0 16 (16)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0052
	Mean (Std)	21.06 (18.22)	8.53 (9.59)	21.06 (18.22)	8.53 (9.59)	12.53 (15.99)	Signed Rank	0.0081
	Median (min;max)	24 (0;56)	7 (0;28)	24 (0;56)	7 (0;28)	11 (-14;39)		
	Q1, Q3 (IQR)	6 37 (31)	0 11 (11)	6 37 (31)	0 11 (11)	0 25 (25)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0065
	Mean (Std)	18.82 (18)	7.06 (7.76)	18.82 (18)	7.06 (7.76)	11.76 (15.5)	Signed Rank	0.0007
	Median (min;max)	14 (0;62)	6 (0;27)	14 (0;62)	6 (0;27)	7 (-2;56)		
	Q1, Q3 (IQR)	6 25 (19)	0 10 (10)	6 25 (19)	0 10 (10)	0 12 (12)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0438
	Mean (Std)	12.71 (15.08)	6.71 (9.6)	12.71 (15.08)	6.71 (9.6)	6 (11.3)	Signed Rank	0.0488
	Median (min;max)	10 (0;50)	0 (0;27)	10 (0;50)	0 (0;27)	0 (-14;37)		
	Q1, Q3 (IQR)	0 15 (15)	0 13 (13)	0 15 (15)	0 13 (13)	0 11 (11)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-217 Change in VAS: ZYN® Smooth 3 mg vs. ZYN® Smooth 3 mg (alt. manu. proc.)

Time point (min)	Statistics	ZS3	ZSA3	Change in ZS3	Change in ZSA3	Change in ZS3 - Change in ZSA3	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)		

Time point (min)	Statistics	ZS3	ZSA3	Change in ZS3	Change in ZSA3	Change in ZS3 - Change in ZSA3	Statistical test	P-value
	Q1, Q3 (IQR)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)		
5	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0979
	Mean (Std)	11.94 (25.19)	2.41 (4.32)	11.94 (25.19)	2.41 (4.32)	9.53 (22.35)	Signed Rank	0.1602
	Median (min;max)	0 (0;90)	1 (0;16)	0 (0;90)	1 (0;16)	0 (-3;74)		
	Q1, Q3 (IQR)	0 6 (6)	0 3 (3)	0 6 (6)	0 3 (3)	0 5 (5)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1847
	Mean (Std)	12.53 (22.66)	5.88 (7.38)	12.53 (22.66)	5.88 (7.38)	6.65 (19.77)	Signed Rank	0.3760
	Median (min;max)	3 (0;70)	4 (0;28)	3 (0;70)	4 (0;28)	0 (-8;70)		
	Q1, Q3 (IQR)	0 14 (14)	0 9 (9)	0 14 (14)	0 9 (9)	0 3 (3)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6592
	Mean (Std)	6.94 (9.24)	7.88 (7.93)	6.94 (9.24)	7.88 (7.93)	-0.94 (8.63)	Signed Rank	0.2321
	Median (min;max)	4 (0;31)	6 (0;32)	4 (0;31)	6 (0;32)	-1 (-12;25)		
	Q1, Q3 (IQR)	0 11 (11)	2 11 (9)	0 11 (11)	2 11 (9)	-6 0 (6)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1057
	Mean (Std)	4.65 (5.54)	8 (8.4)	4.65 (5.54)	8 (8.4)	-3.35 (8.06)	Signed Rank	0.2021
	Median (min;max)	3 (0;18)	6 (0;26)	3 (0;18)	6 (0;26)	0 (-23;6)		
	Q1, Q3 (IQR)	0 7 (7)	0 15 (15)	0 7 (7)	0 15 (15)	-4 0 (4)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6360
	Mean (Std)	5.71 (9.73)	6.65 (8.06)	5.71 (9.73)	6.65 (8.06)	-0.94 (8.04)	Signed Rank	0.7539
	Median (min;max)	2 (0;39)	4 (0;25)	2 (0;39)	4 (0;25)	0 (-17;18)		
	Q1, Q3 (IQR)	0 6 (6)	0 9 (9)	0 6 (6)	0 9 (9)	-5 1 (6)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-218 Change in VAS: ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg

Time point (min)	Statistics	ZS3	ZS6	Change in ZS3	Change in ZS6	Change in ZS3 - Change in ZS6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2258
	Mean (Std)	11.94 (25.19)	4.06 (5.85)	11.94 (25.19)	4.06 (5.85)	7.88 (25.8)	Signed Rank	0.7764
	Median (min;max)	0 (0;90)	1 (0;21)	0 (0;90)	1 (0;21)	0 (-12;87)		
	Q1, Q3 (IQR)	0 6 (6)	0 7 (7)	0 6 (6)	0 7 (7)	-4 3 (7)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6691
	Mean (Std)	12.53 (22.66)	10 (10.81)	12.53 (22.66)	10 (10.81)	2.53 (23.96)	Signed Rank	0.5781
	Median (min;max)	3 (0;70)	7 (0;38)	3 (0;70)	7 (0;38)	0 (-27;63)		
	Q1, Q3 (IQR)	0 14 (14)	1 14 (13)	0 14 (14)	1 14 (13)	-12 4 (16)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2274
	Mean (Std)	6.94 (9.24)	11.35 (12.04)	6.94 (9.24)	11.35 (12.04)	-4.41 (14.49)	Signed Rank	0.1774
	Median (min;max)	4 (0;31)	8 (0;39)	4 (0;31)	8 (0;39)	-2 (-29;31)		
	Q1, Q3 (IQR)	0 11 (11)	2 13 (11)	0 11 (11)	2 13 (11)	13 0 (13)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0514

Time point (min)	Statistics	ZS3	ZS6	Change in ZS3	Change in ZS6	Change in ZS3 - Change in ZS6	Statistical test	P-value
	Mean (Std)	4.65 (5.54)	7.94 (7.72)	4.65 (5.54)	7.94 (7.72)	-3.29 (6.45)	Signed Rank	0.0498
	Median (min;max)	3 (0;18)	7 (0;26)	3 (0;18)	7 (0;26)	0 (-16;6)		
	Q1, Q3 (IQR)	0 7 (7)	0 12 (12)	0 7 (7)	0 12 (12)	-9 0 (9)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.8426
	Mean (Std)	5.71 (9.73)	6.06 (6.21)	5.71 (9.73)	6.06 (6.21)	-0.35 (7.21)	Signed Rank	0.7319
	Median (min;max)	2 (0;39)	4 (0;22)	2 (0;39)	4 (0;22)	0 (-12;17)		
	Q1, Q3 (IQR)	0 6 (6)	0 10 (10)	0 6 (6)	0 10 (10)	-5 0 (5)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-219 Change in VAS: ZYN® Smooth 3 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	ZS3	ZSA6	Change in ZS3	Change in ZSA6	Change in ZS3 - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.4545
	Mean (Std)	11.94 (25.19)	8.25 (13.43)	11.94 (25.19)	8.25 (13.43)	4.31 (22.46)	Signed Rank	0.9336
	Median (min;max)	0 (0;90)	0 (0;44)	0 (0;90)	0 (0;44)	0 (-30;60)		
	Q1, Q3 (IQR)	0 6 (6)	0 12.5 (12.5)	0 6 (6)	0 12.5 (12.5)	-5 1.5 (6.5)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.5966
	Mean (Std)	12.53 (22.66)	9.82 (12.65)	12.53 (22.66)	9.82 (12.65)	2.71 (20.66)	Signed Rank	0.7754
	Median (min;max)	3 (0;70)	7 (0;46)	3 (0;70)	7 (0;46)	0 (-32;64)		
	Q1, Q3 (IQR)	0 14 (14)	0 10 (10)	0 14 (14)	0 10 (10)	-7 0 (7)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.5863
	Mean (Std)	6.94 (9.24)	8.53 (9.59)	6.94 (9.24)	8.53 (9.59)	-1.59 (11.79)	Signed Rank	0.2087
	Median (min;max)	4 (0;31)	7 (0;28)	4 (0;31)	7 (0;28)	-5 (-16;31)		
	Q1, Q3 (IQR)	0 11 (11)	0 11 (11)	0 11 (11)	0 11 (11)	-7 0 (7)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1710
	Mean (Std)	4.65 (5.54)	7.06 (7.76)	4.65 (5.54)	7.06 (7.76)	-2.41 (6.94)	Signed Rank	0.2224
	Median (min;max)	3 (0;18)	6 (0;27)	3 (0;18)	6 (0;27)	0 (-17;9)		
	Q1, Q3 (IQR)	0 7 (7)	0 10 (10)	0 7 (7)	0 10 (10)	-6 1 (7)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6816
	Mean (Std)	5.71 (9.73)	6.71 (9.6)	5.71 (9.73)	6.71 (9.6)	-1 (9.87)	Signed Rank	0.7344
	Median (min;max)	2 (0;39)	0 (0;27)	2 (0;39)	0 (0;27)	0 (-21;23)		
	Q1, Q3 (IQR)	0 6 (6)	0 13 (13)	0 6 (6)	0 13 (13)	-3 0 (3)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-220 Change in VAS: ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg

Time point (min)	Statistics	ZSA3	ZS6	Change in ZSA3	Change in ZS6	Change in ZSA3 - Change in ZS6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2253
	Mean (Std)	2.41 (4.32)	4.06 (5.85)	2.41 (4.32)	4.06 (5.85)	-1.65 (5.38)	Signed Rank	0.1719
	Median (min;max)	1 (0;16)	1 (0;21)	1 (0;16)	1 (0;21)	0 (-11;13)		
	Q1, Q3 (IQR)	0 3 (3)	0 7 (7)	0 3 (3)	0 7 (7)	-4 0 (4)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1453
	Mean (Std)	5.88 (7.38)	10 (10.81)	5.88 (7.38)	10 (10.81)	-4.12 (11.09)	Signed Rank	0.1300
	Median (min;max)	4 (0;28)	7 (0;38)	4 (0;28)	7 (0;38)	-2 (-26;21)		
	Q1, Q3 (IQR)	0 9 (9)	1 14 (13)	0 9 (9)	1 14 (13)	-10 2 (12)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.1539
	Mean (Std)	7.88 (7.93)	11.35 (12.04)	7.88 (7.93)	11.35 (12.04)	-3.47 (9.56)	Signed Rank	0.1992
	Median (min;max)	6 (0;32)	8 (0;39)	6 (0;32)	8 (0;39)	0 (-28;6)		
	Q1, Q3 (IQR)	2 11 (9)	2 13 (11)	2 11 (9)	2 13 (11)	-7 4 (11)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.9739
	Mean (Std)	8 (8.4)	7.94 (7.72)	8 (8.4)	7.94 (7.72)	0.06 (7.28)	Signed Rank	0.6724
	Median (min;max)	6 (0;26)	7 (0;26)	6 (0;26)	7 (0;26)	0 (-12;23)		
	Q1, Q3 (IQR)	0 15 (15)	0 12 (12)	0 15 (15)	0 12 (12)	-3 0 (3)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.7490
	Mean (Std)	6.65 (8.06)	6.06 (6.21)	6.65 (8.06)	6.06 (6.21)	0.59 (7.45)	Signed Rank	0.5737
	Median (min;max)	4 (0;25)	4 (0;22)	4 (0;25)	4 (0;22)	-1 (-7;21)		
	Q1, Q3 (IQR)	0 9 (9)	0 10 (10)	0 9 (9)	0 10 (10)	-4 0 (4)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-221 Change in VAS: ZYN® Smooth 3 mg (alt. manu. proc.) vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	ZSA3	ZSA6	Change in ZSA3	Change in ZSA6	Change in ZSA3 - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.0611
	Mean (Std)	2.41 (4.32)	8.25 (13.43)	2.41 (4.32)	8.25 (13.43)	-5.94 (11.73)	Signed Rank	0.0195
	Median (min;max)	1 (0;16)	0 (0;44)	1 (0;16)	0 (0;44)	0 (-44;2)		
	Q1, Q3 (IQR)	0 3 (3)	0 12.5 (12.5)	0 3 (3)	0 12.5 (12.5)	-7 0 (7)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.0804
	Mean (Std)	5.88 (7.38)	9.82 (12.65)	5.88 (7.38)	9.82 (12.65)	-3.94 (8.71)	Signed Rank	0.0488
	Median (min;max)	4 (0;28)	7 (0;46)	4 (0;28)	7 (0;46)	-2 (-33;9)		
	Q1, Q3 (IQR)	0 9 (9)	0 10 (10)	0 9 (9)	0 10 (10)	-6 0 (6)		

Time point (min)	Statistics	ZSA3	ZSA6	Change in ZSA3	Change in ZSA6	Change in ZSA3 - Change in ZSA6	Statistical test	P-value
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6996
	Mean (Std)	7.88 (7.93)	8.53 (9.59)	7.88 (7.93)	8.53 (9.59)	-0.65 (6.79)	Signed Rank	0.8782
	Median (min;max)	6 (0;32)	7 (0;28)	6 (0;32)	7 (0;28)	0 (-17;11)		
	Q1, Q3 (IQR)	2 11 (9)	0 11 (11)	2 11 (9)	0 11 (11)	-2 4 (6)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.6426
	Mean (Std)	8 (8.4)	7.06 (7.76)	8 (8.4)	7.06 (7.76)	0.94 (8.2)	Signed Rank	0.6216
	Median (min;max)	6 (0;26)	6 (0;27)	6 (0;26)	6 (0;27)	0 (-15;23)		
	Q1, Q3 (IQR)	0 15 (15)	0 10 (10)	0 15 (15)	0 10 (10)	-1 3 (4)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.9781
	Mean (Std)	6.65 (8.06)	6.71 (9.6)	6.65 (8.06)	6.71 (9.6)	-0.06 (8.69)	Signed Rank	0.6523
	Median (min;max)	4 (0;25)	0 (0;27)	4 (0;25)	0 (0;27)	0 (-22;12)		
	Q1, Q3 (IQR)	0 9 (9)	0 13 (13)	0 9 (9)	0 13 (13)	0 3 (3)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-222 Change in VAS: ZYN® Smooth 6 mg vs. ZYN® Smooth 6 mg (alt. manu. proc.)

Time point (min)	Statistics	ZS6	ZSA6	Change in ZS6	Change in ZSA6	Change in ZS6 - Change in ZSA6	Statistical test	P-value
0	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (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)	17 (0)	16 (1)	17 (0)	16 (1)	16 (1)	Student's t	0.2408
	Mean (Std)	4.06 (5.85)	8.25 (13.43)	4.06 (5.85)	8.25 (13.43)	-4.38 (14.33)	Signed Rank	0.5664
	Median (min;max)	1 (0;21)	0 (0;44)	1 (0;21)	0 (0;44)	0 (-44;10)		
	Q1, Q3 (IQR)	0 7 (7)	0 12.5 (12.5)	0 7 (7)	0 12.5 (12.5)	-5.5 3 (8.5)		
10	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.9596
	Mean (Std)	10 (10.81)	9.82 (12.65)	10 (10.81)	9.82 (12.65)	0.18 (14.14)	Signed Rank	0.5012
	Median (min;max)	7 (0;38)	7 (0;46)	7 (0;38)	7 (0;46)	2 (-36;20)		
	Q1, Q3 (IQR)	1 14 (13)	0 10 (10)	1 14 (13)	0 10 (10)	-1 7 (8)		
15	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.2787
	Mean (Std)	11.35 (12.04)	8.53 (9.59)	11.35 (12.04)	8.53 (9.59)	2.82 (10.38)	Signed Rank	0.2905
	Median (min;max)	8 (0;39)	7 (0;28)	8 (0;39)	7 (0;28)	4 (-21;21)		
	Q1, Q3 (IQR)	2 13 (11)	0 11 (11)	2 13 (11)	0 11 (11)	0 8 (8)		
30	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.4453
	Mean (Std)	7.94 (7.72)	7.06 (7.76)	7.94 (7.72)	7.06 (7.76)	0.88 (4.65)	Signed Rank	0.2227
	Median (min;max)	7 (0;26)	6 (0;27)	7 (0;26)	6 (0;27)	0 (-13;9)		
	Q1, Q3 (IQR)	0 12 (12)	0 10 (10)	0 12 (12)	0 10 (10)	0 3 (3)		
60	n (nmiss)	17 (0)	17 (0)	17 (0)	17 (0)	17 (0)	Student's t	0.7518
	Mean (Std)	6.06 (6.21)	6.71 (9.6)	6.06 (6.21)	6.71 (9.6)	-0.65 (8.29)	Signed Rank	1.0000
	Median (min;max)	4 (0;22)	0 (0;27)	4 (0;22)	0 (0;27)	0 (-17;12)		
	Q1, Q3 (IQR)	0 10 (10)	0 13 (13)	0 10 (10)	0 13 (13)	-1 5 (6)		

SM17_03 Analysis of secondary endpoint - VAS, SAS program: sec_endpoint_vas.sas. Run by: Fredrik Hansson, fredrik.hansson@ctc-ab.se 2018-03-21T01:22:13

Table 14.3-223 Subjective nicotine effect by treatment

Assessment	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
Subjective nicotine effect (VAS rating)	Measured value	ZYN® Smooth 3 mg	Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	0	90	11.9	0	25.2
			Timepoint 0:10	17	0	70	12.5	3	22.7
			Timepoint 0:15	17	0	31	6.94	4	9.24
			Timepoint 0:30	17	0	18	4.65	3	5.54
			Timepoint 1:00	17	0	39	5.71	2	9.73
		ZYN® Smooth 6 mg	Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	0	21	4.06	1	5.85
			Timepoint 0:10	17	0	38	10	7	10.8
			Timepoint 0:15	17	0	39	11.4	8	12
			Timepoint 0:30	17	0	26	7.94	7	7.72
			Timepoint 1:00	17	0	22	6.06	4	6.21
		ZYN® Smooth 3 mg (alt. manu. proc.)	Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	0	16	2.41	1	4.32
			Timepoint 0:10	17	0	28	5.88	4	7.38
			Timepoint 0:15	17	0	32	7.88	6	7.93
			Timepoint 0:30	17	0	26	8	6	8.4
			Timepoint 1:00	17	0	25	6.65	4	8.06
		ZYN® Smooth 6 mg (alt. manu. proc.)	Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	16	0	44	8.25	0	13.4
			Timepoint 0:10	17	0	46	9.82	7	12.7
			Timepoint 0:15	17	0	28	8.53	7	9.59
			Timepoint 0:30	17	0	27	7.06	6	7.76
			Timepoint 1:00	17	0	27	6.71	0	9.6
		Swedish portion snus PSWL 1.0 g (8 mg)	Timepoint 0:00	17	0	0	0	0	0

Assessment	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
Absolute change from pre-dose baseline	ZYN® Smooth 3 mg		Timepoint 0:05	17	0	56	12.6	9	16.1
			Timepoint 0:10	17	0	60	17.8	17	15.3
			Timepoint 0:15	17	0	56	21.1	24	18.2
			Timepoint 0:30	17	0	62	18.8	14	18
			Timepoint 1:00	17	0	50	12.7	10	15.1
			Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	0	90	11.9	0	25.2
			Timepoint 0:10	17	0	70	12.5	3	22.7
			Timepoint 0:15	17	0	31	6.94	4	9.24
			Timepoint 0:30	17	0	18	4.65	3	5.54
			Timepoint 1:00	17	0	39	5.71	2	9.73
			Timepoint 0:00	17	0	0	0	0	0
	ZYN® Smooth 6 mg		Timepoint 0:05	17	0	21	4.06	1	5.85
			Timepoint 0:10	17	0	38	10	7	10.8
			Timepoint 0:15	17	0	39	11.4	8	12
			Timepoint 0:30	17	0	26	7.94	7	7.72
			Timepoint 1:00	17	0	22	6.06	4	6.21
			Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	0	16	2.41	1	4.32
			Timepoint 0:10	17	0	28	5.88	4	7.38
			Timepoint 0:15	17	0	32	7.88	6	7.93
			Timepoint 0:30	17	0	26	8	6	8.4
			Timepoint 1:00	17	0	25	6.65	4	8.06
			Timepoint 0:00	17	0	0	0	0	0
	ZYN® Smooth 3 mg (alt. manu. proc.)		Timepoint 0:05	16	0	44	8.25	0	13.4
			Timepoint 0:10	17	0	46	9.82	7	12.7
			Timepoint 0:15	17	0	28	8.53	7	9.59
	ZYN® Smooth 6 mg (alt. manu. proc.)		Timepoint 0:05	16	0	44	8.25	0	13.4
			Timepoint 0:10	17	0	46	9.82	7	12.7
			Timepoint 0:15	17	0	28	8.53	7	9.59

Assessment	Result Category	Treatment	Planned Time Point Name	N	Min	Max	Mean	Median	Std
		Swedish portion snus PSL 1.0 g (8 mg)	Timepoint 0:30	17	0	27	7.06	6	7.76
			Timepoint 1:00	17	0	27	6.71	0	9.6
			Timepoint 0:00	17	0	0	0	0	0
			Timepoint 0:05	17	0	56	12.6	9	16.1
			Timepoint 0:10	17	0	60	17.8	17	15.3
			Timepoint 0:15	17	0	56	21.1	24	18.2
			Timepoint 0:30	17	0	62	18.8	14	18
			Timepoint 1:00	17	0	50	12.7	10	15.1

Data based on PPS population

SM17_03 QS tabulations, SAS program: safety_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T15:57:33

14.4 Adverse events

14.4.1 Displays of adverse events

Table 14.4-1 *Serious treatment emergent AE: number of subjects with at least one SAE, by treatment*

Treatment	n
No SAE	18

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

Table 14.4-2 *Serious treatment emergent AE: number of subjects with at least one related SAE, by treatment*

Number of subjects with no related SAE		
Treatment	n	%
No SAE	18	100.0%

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

Table 14.4-3 *Baseline AE: number of AE*

Treatment	Number of AE:s
Pre-treatment	3
Total	3

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

Table 14.4-4 *Baseline AE: number of subjects with at least one AE*

Treatment	n
No AE	15
Pre-treatment	3

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

Table 14.4-5 *Baseline AE: subject unique AE:s by MedDRA body class*

Body System or Organ Class	Treatment	
	Pre-treatment (N=18)	
	Number of subjects	% of subjects
Infections and infestations	2	11.1%
Nervous system disorders	1	5.6%

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

Table 14.4-6 Baseline AE: subject unique AE:s by MedDRA body class and PT

Body System or Organ Class	Dictionary-Derived Term	Treatment	
		Pre-treatment (N=18)	
		Number of subjects	% of subjects
Infections and infestations	Nasopharyngitis	1	5.6%
	Rhinitis	1	5.6%
Nervous system disorders	Headache	1	5.6%

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

Table 14.4-7 Baseline AE: subject unique AE:s by relation to study product and MedDRA body class and PT

Body System or Organ Class	Dictionary-Derived Term	Causality	Treatment	
			Pre-treatment (N=18)	
			Number of subjects	% of subjects
Infections and infestations	Nasopharyngitis	UNKNOWN	1	5.6%
	Rhinitis	UNKNOWN	1	5.6%
Nervous system disorders	Headache	UNKNOWN	1	5.6%

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

Table 14.4-8 Serious baseline AE: number of subjects with at least one SAE

Treatment	n
No SAE	18

SM17_03 AE tabulations, SAS program: ae_tabulations.sas. Run by: Calle Joachimsson, calle.joachimsson@ctc-ab.se 2018-03-28T14:34:38

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..
- 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
- 16.2.2 Protocol deviations
- 16.2.3 Subjects excluded from the (efficacy) analysis
- 16.2.4 Demographic data and other baseline characteristics
- 16.2.5 Compliance and/or drug concentration data
- 16.2.6 Pharmacokinetic, extraction and response data
- 16.2.7 AE listings
- 16.2.8 Listing of individual laboratory measurements by subject

16.3 Case report forms

- 16.3.1 CRFs for deaths, other SAEs and withdrawals for AE (not applicable)
- 16.3.2 Other CRFs submitted (not applicable)

16.4 Individual subject data listings (US archival listings) (available upon request)

Appendix 16 is provided as a separate document to the CSR.