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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE(s)	adverse event(s)
AMP	alternative manufacturing process
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{60min}	area under the plasma concentration-time curve from time zero to 60 minutes
$AUC_{0\text{-}last}$	area under the plasma concentration-time curve from time zero to last observation
$AUC_{(0120)}$	area under the plasma concentration-time curve from time zero to 120 minutes
B(a)P	benzo(a)pyrene
bpm	beats per minute
CI	confidence interval
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
ENDS	Electronic Nicotine Delivery Systems
FAS	full analysis set
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GI	gastrointestinal
HPHC	harmful and potentially harmful constituent
IHD	ischemic heart disease
IP	investigational product
MI	myocardial infarction
MRTPA	Modified Risk Tobacco Product Application
MTSS	Motivation to Stop Scale
NNN	N-nitrosonornicotine
NNK	(4-methylnitrosamino)-1-(3-pyridyl)-1-butanone
NRT	nicotine replacement therapy
PAH	polycyclic aromatic hydrocarbons
PATH	Population Assessment of Tobacco and Health
PCI	percutaneous coronary intervention
PK	Pharmacokinetic(s)
PMTA	Premarket Tobacco Product Application
PPS	per-protocol analysis set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSWL	portion snus white large
RR	relative risk
SAE	serious adverse event
SD	standard deviation

SOC	System Organ Class
ST	smokeless tobacco
$t_{½}$ (z)	terminal half-life
t_{max}	time to maximum concentration
TNP	tobacco/nicotine product
TSNAs	tobacco-specific nitrosamines
US	United States
VAS	visual analog scale

1 INTRODUCTION

Swedish Match USA, Inc. (hereafter referred to as Swedish Match) is submitting this Premarket Tobacco Product Application (PMTA) for ZYN®, in accordance with the requirements under Section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). ZYN is currently marketed in the United States (US), Sweden, Denmark, and select locations in Europe. Although ZYN has been marketed in the US since 2014 (ie, prior to 08 August 2016), the product is a "new tobacco product" under Section 910(a)(1) of the FD&C Act in that it was not commercially marketed in the US as of 15 February 2007.

This summary presents scientific evidence demonstrating that the ZYN products are "appropriate for the protection of the public health" (Section 910[c](2)[A] of the FD&C Act) regarding the risks and benefits to the population as a whole, including users and non-users of ZYN as part of this PMTA.

1.1 Product and Relevant Comparator

ZYN is a non-heated, tobacco-free, smoke-free, and spit-free nicotine pouch for oral use and has an appearance similar to Swedish snus products. The product is intended for adult tobacco and nicotine consumers. Use of ZYN does not involve any inhalation of smoke or vapor. ZYN comes in 10 different flavors (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Citrus, Smooth, Chill, and Fresh) and two nicotine strengths (3 and 6 mg per pouch). ZYN is intended to be used under the upper lip for up to 60 minutes and is then discarded. Therefore, exposure to harmful and potentially harmful constituents (HPHCs) only involves those that are taken up through the oral, mucous membranes, or extracted to the saliva that is subsequently swallowed.

In the absence of other relevant Food and Drug Administration (FDA) guidance documents, the Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS) Guidance for Industry (June 2019) (FDA PMTA ENDS Guidance 2019) is relied on for this PMTA because the guidance can be applied to a smokeless nicotine product, such as ZYN. In addition, this application is also reflective of the proposed rule for PMTAs (FDA Proposed Rule 2019).

In terms of health effects, a reasonable comparator to ZYN is cigarettes as cigarette smoking accounts for the vast majority of tobacco-related morbidity and pre-term mortality in the US and by far represent the most commonly used tobacco product on the US market. In the PMTA ENDS Guidance, the FDA recommends that a new product should be compared to an existing product within the same category. Consumer data from Study (b) (4) shows that moist snuff was the most commonly used tobacco product weeks before starting ZYN use. Therefore, in this PMTA, ZYN is also compared with existing moist snuff products in the US market.

Bridging to Swedish snus products is relevant since the products are similar in terms of use topography. There is also an abundance of human health data for snus based on long-term, epidemiological studies. The HPHC content in ZYN is typically much lower than that in snus. In fact, many of the HPHCs that are considered to be the most toxicologically relevant in snus are below the level of detection in ZYN. These include tobacco specific nitrosamines and polycyclic aromatic hydrocarbons (PAH) such as benzpyrene. The similarities between ZYN and snus in regard to use of topography and systemic nicotine exposure, together with the consistently lower

levels of HPHCs in ZYN, clearly illustrate that the health effect profile of snus can be used as a "worst case scenario" for ZYN. As noted in the FDA Modified Risk Tobacco Product Application (MRTPA) Technical Project Lead (TPL) Review 2019, "The applicant **has demonstrated** that, as actually used by consumers, the eight General Snus products sold or distributed with the proposed modified risk information will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. The claim 'Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis' is scientifically accurate."

Both the ZYN and General Snus products can be categorized as smokeless pouch products, are used in the same way (between the gum and the upper lip), and are similar in shape and size (although ZYN is slightly smaller). Both products are manufactured by the same company. The snus products to which the ZYN products are compared are produced under Swedish Match proprietary quality standard GOTHIATEK®. The ZYN products are produced under a quality management system ensuring that almost none of the HPHCs, which are governed by the GOTHIATEK standard, can be detected in the ZYN products.

As noted in the FDA PMTA TPL Review 2015, Section V. Conclusions and Recommendations, the topline reasons for granting PMTA marketing authorization of General Snus included the following:

- GOTHIATEK quality system as described above
- The General Snus products have significantly lower levels of the most likely carcinogenic constituents in tobacco products (N-nitrosonornicotine [NNN] and (4-methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) compared to >97% in the smokeless tobacco products currently on US market.
- The levels of other HPHCs in General Snus are similar to or lower than the levels in other smokeless tobacco products.
- When used exclusively instead of other US market smokeless tobacco products or cigarettes, General Snus offers potential for reductions in oral cancer.
- When used exclusively instead of cigarettes, General Snus offers lower risk of developing respiratory diseases (ie, chronic obstructive pulmonary disease [COPD], emphysema, chronic bronchitis) and certain cancers (such as oral, esophageal, and lung).
- It is anticipated that there is a low likelihood of non-user uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

Therefore, this PMTA presents a full assessment of ZYN, demonstrating that bridging to the science on snus is relevant since it compares favorably to General Snus and thus that marketing of the product is appropriate for the protection of the public health.

In addition, as noted in the FDA Modified Risk Tobacco Product Application (MRTPA) Technical Project Lead (TPL) Review 2019 for General Snus:

- "In sum, FDA's assessment of the scientific evidence supports the conclusion that exclusive users of snus have lower risk relative to cigarette smokers for each of these health outcomes: mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. This assessment supports the revised modified risk claim as scientifically accurate. Overall, the available scientific evidence demonstrates that the products that are the subject of these applications, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users."
- "Subsequent to the completion of FDA's review, Rostron and colleagues (2018) conducted a systematic review and meta-analysis of studies pertaining to smokeless tobacco use and circulatory disease risk, providing a more comprehensive examination of this relationship, including more recent data (e.g., Timberlake et al., 2017). Based on this review, risk of ischemic heart disease was not increased in Swedish studies of current smokeless tobacco users who were never smokers (vs. non-users) (RR=1.04, 0.93-1.16, n=3), but was significantly increased in U.S. studies of smokeless tobacco users who were never smokers (RR=1.17, 95% 1.08-1.27, n=3). By comparison…cigarette smoking has been found to increase risk of cardiovascular disease by a factor of about 1.5- to 3-fold. This most recent review provides clear evidence that the heart disease risks due to Swedish snus use are lower than the risks from cigarette smoking."

1.2 HPHCs and Biomarkers of Harm/Exposure

Full details of the HPHCs present in ZYN compared to General Snus is set forth in Section G.5 Nonclinical Evaluation Summary, Section 4. Typically, the levels in ZYN are substantially lower than in snus and thus even more reduced as compared to US moist snuff products. In fact, several of the toxicologically most relevant HPHCs cannot be detected in ZYN (eg, NNN, NNK, and benzopyrene). Moreover, *in vitro* testing demonstrated the overall safety of all 10 flavors of ZYN 6 mg as the studies showed no mutagenic or genotoxic response (Section G.5 Nonclinical Evaluation Summary, Section 5).

In its evaluation of HPHCs in the General Snus PMTAs (FDA PMTA TPL Review 2015), FDA focused mainly on NNN and NNK and noted that the "products contain significantly lower levels of NNN and NNK compared to over 97% in the smokeless tobacco (ST) products currently on US market. Since NNN and NNK are likely among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers using ST products. Assuming persons who would have used other US ST products use these product instead, an individual using these products with reduced NNN levels could decrease the excess cancer risk by 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of United States (US)-style snus, and 92% compared to use of dry snuff. Even further reductions in excess cancer risk could occur with the corresponding reductions in NNK; however, a quantitative contribution cannot be determined at this time due to the absence of a NNK cancer slope factor." No threshold level has been set for NNN and NNK in relation to the risk of cancer from a toxicologic standpoint. However, the levels of carcinogenic substances, such as tobacco-specific nitrosamines (TSNAs) (eg, NNN and NNK) and benzo(a)pyrene (B[a]P), are not quantifiable in ZYN, whereas General Snus contains low levels of TSNAs and B(a)P.

In the FDA PMTA ENDS Guidance 2019, FDA recommends testing for HPHCs and biomarkers of harm/exposure (eg, cotinine, NNN). However, ZYN contains no nitrosamines or polycyclic hydrocarbons. Out of the 93 HPHCs identified in cigarette smoke only 20 are present in General Snus. Of the 45 HPHCs tested for ZYN, 37 were below the limit of quantification. The levels of the remaining HPHCs in ZYN were lower (acetaldehyde, nitrite, nornicotine, and propylene glycol) or almost always lower (naphthalene, which was increased in ZYN Citrus only) than those in General Snus, and there was an HPHC specific to a flavoring substance (coumarin in ZYN Cinnamon only) (Section G.5 Nonclinical Evaluation Summary, Section 4). Only formaldehyde was found at levels slightly higher than in snus. However, by comparing the actual exposure against valid threshold limit values set by recognized authorities in a quantitative risk assessment, the low levels of formaldehyde, which is considered a HPHC only when inhaled, and the few other HPHCs that were detected in ZYN products are not likely to have adverse effects on public health (exposure is well under current acceptable daily intake levels and tolerable daily intake levels). Thus, the toxicological safety profile of ZYN represents a significant improvement over snus and thus even more so over the cigarettes and moist snuff products available on the US market.

The nicotine content of ZYN (3 or 6 mg) is lower compared to the General Snus products (8 mg), which received PMTA marketing authorizations (PM0000011 - PM0000017) on 10 November 2015 and modified risk orders (MR0000020 – MR0000022, MR0000024 – MR0000025, and MR0000027 – MR0000029) on 22 October 2019. As noted in the FDA PMTA TPL Review 2015, “these nicotine values are within the reported ranges from other marketed US moist snuff.” Nicotine pharmacokinetic (PK) studies on ZYN are provided as part of this application.

Therefore, Swedish Match did not measure any biomarkers of harm/exposure other than nicotine in any of the clinical studies.

1.3 Information Included in This Document to Support the PMTA

This document summarizes all clinically related research findings, including the product’s health risks, the product’s effect on tobacco use behavior among current users, the product’s effect on tobacco use initiation among non-users, and the product’s effect on the population as a whole. The summary includes findings from clinical studies conducted with ZYN, supplemented by data from the published literature. Key questions from the PMTA ENDS Guidance addressed in this summary and the corresponding location in the document are provided in Table 1.

Table 1 Key Questions From the PMTA ENDS Guidance and Location in This Document

Key Question	Location
Summary of the clinical studies relevant to the PMTA	Section 4 (overall), Section 5.1 (PK), Section 5.2 (pharmacodynamics), Section 6 (safety)
The relative health risks of the product for both users and non-users compared to other tobacco products on the market, including tobacco products within the same product category as it may be expected that consumers of current products within the same product category may switch to using a newly marketed product, and the health risks compared to never using tobacco products	Section 7.7
The use patterns within which consumers are likely to use the product	Sections 7.3 and 7.5
The likelihood, based on the research information contained in your application, of current non-users of tobacco products initiating or reinitiating tobacco use by using the product	Sections 7.6.1 and 7.6.3
The likelihood, based on the research information contained in your application, that consumers will adopt the product and then switch to other tobacco products that may present higher levels of risk, such as cigarettes	Sections 7.6.2 and 7.6.5
The likelihood, based on the research information contained in your application, of consumers using the product in conjunction with other tobacco products	Section 7.6.6
The likelihood, based on the research information contained in your application, of current tobacco product users switching to the product instead of ceasing tobacco product use or using an FDA-approved tobacco cessation product (because use of the product includes inherent risks above quitting altogether or the use of an FDA-approved NRT)	Sections 7.6.7 and 7.6.8
Assessment of abuse liability (ie, the addictiveness, abuse, and misuse potential of the new product and the exposure to nicotine during product use)	Sections 5.2.2, 5.3, and 7.8
Assessment of user topography (how individual users consume the product), the frequency with which consumers use the product, and the trends by which users consume the product over time	Sections 7.1 and 7.2
A discussion demonstrating how the data and information contained in your PMTA establish that permitting the marketing of the new tobacco product would be APPH	Section 9

APPH=appropriate for the protection of public health; ENDS=Electronic Nicotine Delivery Systems; FDA=Food and Drug Administration; NRT=nicotine replacement therapy; PK=pharmacokinetics; PMTA=Premarket Tobacco Product Application.

2 SYSTEMATIC LITERATURE REVIEW ON HEALTH EFFECTS AND USE BEHAVIOR

Swedish Match began selling ZYN in 2014, and to date, there is no published literature on the use of ZYN. As ZYN exposes the user to similar levels of nicotine to those found in snus but generally has reduced or non-measurable levels of unwanted HPHCs, health effects of snus could be considered to be a measure of maximum health risks. A systematic literature review was therefore performed on Swedish snus as follows:

- health effects of Swedish snus, both absolute and relative to cigarette smoking, as well as *in vitro* and *in vivo* toxicology studies of Swedish snus
- tobacco use behaviors and perceptions of risk pertaining to the use of Swedish snus

The systematic literature review was performed as part of an update to the Section I.1 2013 Environ Report, which was previously conducted for the General Snus PMTA and MRTPA and included a comprehensive review of the available literature on snus through December 2012 and also selected important new publications as available through April 2013.

Search Methods

Relevant literature included publications that have been published and/or made publicly available after 01 December 2012 (ie, the cut-off date for the MRTPA search) and were not included in the 2013 Environ Report. Structured searches in PubMed/MedLine (http://www.pubmed.com), Scopus (http://www.scopus.com/), and ClinicalTrials.gov (http://clinicaltrials.gov/) were used to identify the relevant literature spanning across the disciplines and publication types of interest. Additionally, searches of select, pre-determined government and non-government organization websites were also conducted to identify reports of primary data not traditionally captured in literature databases.

In addition, a retrospective literature search on the human health effects of Swedish snus was conducted without a start date through 01 December 2012. This was motivated by the lack of a reproducible systematic approach regarding the literature search strategy described in the 2013 Environ Report. Any potentially relevant studies identified through this search that were not included in the 2013 Environ Report were evaluated and included in the update if deemed relevant.

All searches were completed on 28 July 2017.

When relevant, additional literature published after 28 July 2017 was included.

2.1 Health Effects

The objective of the update relating to the health effects for this PMTA was to identify and evaluate all original primary scientific studies published since 01 December 2012 through 28 July 2017, and not included in the previous review, and to comprehensively update previous conclusions contained within the following specific sub-sections of the 2013 Environ Report:

- Section 4: Non-clinical toxicological studies with snus
- Section 5: Human health effects of snus (including all previous and new endpoints)
- Appendix VI (to Section 5): Relative risks among snus users and smokers compared to nontobacco users
- Appendix VII (to Section 5): Comparison of risks from dual use, switching, and quitting

The updated report (Section I.1 Health Effects and Meta-Analysis Update Report) includes a summary of the conclusions from the document listed above (which is comprehensive through December 2012), a presentation of new information (if available) for each endpoint, and an updated evaluation of the total available evidence and conclusion. Newly identified human health endpoints were presented with their own new summary, evaluation, and conclusion. This review and update of the 2013 Environ Report was intended to be systematic, with the methods clearly and transparently presented so the literature searches and evaluations could be replicated. This systematic review was intended to comply with all relevant guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, a well-established and highly regarded standard for the reporting of systematic reviews and meta-analyses. The 27-item checklist of the protocol is provided in Section I.1 Health Effects and Meta-Analysis Update Report, Appendix A, with relevant page numbers cited for each item on the checklist.

Full details on the search strategy and methods are provided in Section I.1 Health Effects and Meta-Analysis Update Report, Section 1. Methods and search results are detailed in Section I.1 Health Effects and Meta-Analysis Update Report, Section 1.2. Detailed screening results of the literature searches are provided in an adapted PRISMA inclusion/exclusion diagram in Section I.1 Health Effects and Meta-Analysis Update Report, Appendix C. After detailed screening and review, the following were identified and included in the qualitative syntheses, 47 relevant primary studies on the human health effects of Swedish snus (including two additional studies identified from the retrospective literature search through 01 December 2012).

2.2 Use Behavior

The objective of the update relating to the use behavior and risk perceptions for this PMTA was to identify and evaluate all original primary scientific studies published since 01 December 2012 through 28 July 2017 and not included in the previous review, and to comprehensively update previous conclusions contained within the following specific sub-sections of the 2013 Environ Report:

- Section 6.2: Effect on tobacco use behavior among current users
- Section 6.3: Effect on tobacco use initiation among non-users
- Sections 6.4.1.1 to 6.4.1.2: Consumers' beliefs about the health risks of using the product

The updated report (Section I.1 Use Behavior Update Report) includes a summary of the conclusions from the sections of the 2013 Environ Report listed above (which are comprehensive through 01 December 2012), a presentation of new information (if available) for each topic, and an updated evaluation of the total available evidence and conclusion.

Full details on the search strategy and methods are provided in Section I.1 Use Behavior Update Report, Section 1. Methods and search results are detailed in Section I.1 Use Behavior Update Report, Section 1.2. Detailed screening results of the literature searches are provided in an adapted PRISMA inclusion/exclusion diagram in Section I.1 Use Behavior Update Report, Appendix B. After detailed screening and review, the following were identified and included in the qualitative syntheses, 23 relevant primary studies on use behavior and risk perceptions related to Swedish snus.

3 HEALTH EFFECTS

There is no literature on the health effects of ZYN. As ZYN exposes the user to similar levels of nicotine to those found in snus but generally has reduced or non-measurable levels of unwanted HPHCs and does not involve any significant HPHC exposure that is specific to ZYN, the health effects of snus could be considered to be a measure of maximum health risks.

As noted in the FDA Modified Risk Tobacco Product Application (MRTPA) Technical Project Lead (TPL) Review 2019 for General Snus, "In the scientific review of the original applications, epidemiological studies provided the strongest evidence for assessing the long-term health risk of Swedish snus use as compared to the risks from cigarette smoking. Although the epidemiological literature is not product specific, the body of literature from Sweden and Norway is particularly relevant to the assessment of the long-term health risks of the General Snus products that are the subject of these MRTPAs, as noted in the 2016 TPL review (p.33):

> Many, if not all, of the studies included in the modified risk applications for the General Snus products did not include the specific products that are the subject of the applications. Rather, the studies included products that were available in Sweden and Norway. SMNA justifies the use of the studies by asserting that during the period of study…FDA's review of the eight General Snus products confirms that the eight General snus products also conform to the GOTHIATEK® standard. It is reasonable to expect that General Snus products, when used in a manner similar to that observed in the submitted

studies, would result in similar exposures and potential health effects as those reported in those studies."

Therefore, a systematic review of the literature on the health effects of snus was conducted, and results are summarized in this PMTA for the following health conditions:

- Oral safety (Section 3.1)
- Cancer risk (Section 3.2)
- Cardiovascular effects (Section 3.3)
- Metabolic effects (Section 3.4)
- Gastrointestinal (GI) effects (Section 3.5)
- Other health effects (Section 3.6)
- All-cause mortality (Section 3.7)
- Pregnancy outcomes and reproductive effects (Section 3.8)
- Health risks of dual use and switchers compared to smoking (Section 3.9)

3.1 Non-Neoplastic Oral Effects

A systematic review of the literature was conducted on the health effects of snus on non-neoplastic oral effects, including gingivitis, gingival recession, periodontal disease, oral mucosal effects, and other dental conditions (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.2). Results are summarized as follows:

- There is limited/suggestive evidence of no association between snus use and dental caries, tooth loss, gingivitis, and periodontal disease.
- There is inadequate/insufficient evidence to determine whether an association exists between snus use and tooth wear, gingival recession, leukoplakia, dysplasia, oral melanin pigmentation, or p-53 protein expression levels in oral lesions.
- There is a general consensus from the available literature that Swedish snus causes a characteristic type of oral mucosal lesion (Snuff Dipper's Lesion); and in this causal relationship, there is sufficient evidence of an association. However, the literature also demonstrate that the oral mucosal lesion caused by snus use typically regresses within a few weeks following cessation of snus use, and among long-time users who do not change their snus habits, presents no evidence that they progress to cancer, even with long-term use.

3.2 Cancer Risk

TSNAs (eg, NNN and NNK) and B(a)P are considered to be the most likely carcinogenic constituents in tobacco. Importantly, the levels of carcinogenic substances including TSNAs and B(a)P are not quantifiable in ZYN (Section G.5 Nonclinical Evaluation Summary), whereas General Snus contains low levels of TSNAs and B[a]P. Therefore, cancer risk is assumed to be lower with ZYN than with General Snus, which in turn has been determined by the FDA to be associated with lower cancer risk than cigarettes and moist snuff. As noted in the FDA PMTA TPL Review 2015, Section V. Conclusions and Recommendations, FDA concluded that:

- When used exclusively instead of other US market smokeless tobacco products or cigarettes, General Snus offers potential for reductions in **oral cancer**.

- When used exclusively instead of cigarettes, General Snus offers lower risk of developing respiratory diseases (ie, COPD, emphysema, and chronic bronchitis) and **certain cancers (such as oral, esophageal, and lung)**.

A systematic literature review was conducted on the risk of cancer (including head and neck, pancreatic, stomach, colorectal and anal, kidney and bladder, lung, skin and melanoma, and hematopoietic) with snus use (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.3). Meta-analyses and statistical comparisons of the health risks of snus and cigarette use were also conducted for all cancers as well as head and neck cancer, pancreatic cancer, stomach cancer, and lung cancer; results are summarized by cancer type in this section.

All Cancers

Two studies were identified during the review and provided limited/suggestive evidence of no association between snus use and cancer (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.3.10).

Head and Neck Cancer

Head and neck cancer consists of oral, pharyngeal, laryngeal, and esophageal cancer.

Oral and Pharyngeal Cancer

Smoking accounts for 64% of all oral and pharyngeal cancer deaths in the US, constituting 1.2% of all smoking-attributable deaths (CDC 2008). Overall, the evaluation of the literature found that the available studies provide limited/suggestive evidence of no association between snus use and oral and pharyngeal cancer (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.1.2). In general, a statistically significantly lower risk of oral cancer was found in snus users compared to smokers (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.1.3).

Esophageal Cancer

Smoking accounts for 68% of all esophageal cancer deaths in the US, constituting 2.2% of all smoking-attributable deaths (CDC 2008). Overall, the evaluation of the literature found that the available studies provide balanced/mixed evidence of an association between snus use and esophageal cancer (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.1.4). Even though a lower magnitude of risk of esophageal cancer was found for snus users compared with smokers, the statistical significance of this magnitude is unclear.

Esophageal Squamous Cell Carcinoma

The evaluation of the literature found that the available studies provide balanced/mixed evidence of an association between snus use and squamous cell carcinoma (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.1.5).

Esophageal Adenocarcinoma

The evaluation of the literature found that the available studies provide limited/suggestive evidence of no association between snus use and adenocarcinoma (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.1.6). Even though a lower magnitude of risk of adenocarcinoma was found for snus users compared with smokers, the statistical significance of this magnitude is unclear.

Pancreatic Cancer

Smoking accounts for 22% of all pancreatic cancer deaths in the US, constituting 1.7% of all smoking-attributable deaths (CDC 2008). The evaluation of the literature found that the available studies provide limited/suggestive evidence of no association between snus use and pancreatic cancer, and a statistically significantly lower risk of pancreatic cancer was found in snus users compared to smokers (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.2).

Stomach Cancer

Smoking accounts for 21% of all stomach cancer deaths in the US, constituting 0.6% of all smoking-attributable deaths (CDC 2008). The evaluation of the literature found that the available studies provide limited/suggestive evidence of no association between snus use and overall and cardia stomach cancer (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.3). However, the available studies provided inadequate/insufficient evidence to determine whether an association exists between snus use and non-cardiac stomach cancer. A statistically non-significant decreased risk of stomach cancer was also found in snus users compared to smokers.

Lung Cancer

Smoking accounts for 80% of all lung cancer deaths in the US, constituting 32% of all smoking-attributable deaths (CDC 2008). The evaluation of the literature found that the available studies provide limited/suggestive evidence of no association between snus use and lung cancer, and a statistically significantly lower risk of lung cancer was found in snus users compared to smokers (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.4.4).

3.3 Cardiovascular Effects

A systematic review of the literature was conducted on the health effects of snus on cardiovascular disease (CVD) (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.4 and Section 3.5). Smoking accounts for overall 16% of all ischemic heart disease (IHD) deaths in the US, constituting 32.7% of all smoking-attributable deaths (CDC 2008). The qualitative evaluation of the literature found that the available studies provide:

- Limited/suggestive evidence of no association between snus use and incident IHD, myocardial infarction (MI), or heart failure.
- Balanced/mixed evidence of an association between snus use and fatal MI or sudden cardiac death.
- Limited/suggestive evidence of no association between snus use and incident CVD.
- Balanced/mixed evidence of an association between snus use and fatal CVD.
- Limited/suggestive evidence of no association between snus use and atrial fibrillation.
- Limited/suggestive evidence of no association between snus use and incident stroke, including the subtypes: ischemic and hemorrhagic.
- Balanced/mixed evidence of an association between snus use and fatal stroke and its subtypes.

Based on available evidence, a significantly lower risk of incident IHD and MI as well as fatal IHD and MI was found for snus users compared to smokers (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.5.4 and Section 3.5.5). A lower magnitude of risk of incident stroke for snus users compared with smokers was also found; however, the statistical significance of this magnitude is unclear (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.5.6).

In a recently published meta-analysis of 17 cohort studies (11 from Sweden; 6 from the US), two pooled analyses (from Sweden), five case-control studies (from Sweden), and one cross-sectional analysis (from the US), Rostron et al also found no increased risk of IHD or stroke in Swedish studies among current or former snus users compared with non-users (Rostron et al 2018). However, in the US, the authors found an increased risk of heart disease (relative risk [RR]: 1.17, 95% confidence interval [CI]: 1.09 to 1.27) and stroke (RR: 1.28, 95% CI: 1.01 to 1.62) among current smokeless tobacco users compared with non-users. These results in US current smokeless tobacco users were consistent with those in US ever smokeless tobacco users. As noted by the authors, the observed differences in results between Sweden and the US may be due to the fact that US smokeless tobacco products are known to contain varying levels of nicotine, NNN, NNK, other TSNAs, and B(a)P, whereas Swedish snus products have generally lower levels of NNN, NNK, other TSNAs, and B(a)P.

In another recently published analysis of a large real-world Swedish population of almost 75,000 patients admitted for a first percutaneous coronary intervention (PCI) between 2009 and 2018, snus use at admission was not associated with a higher occurrence of all-cause mortality, new revascularization, or heart failure hospitalization at 1 year (Frobert et al 2019). Compared with quitters, a shorter duration to subsequent PCI in snus users who continued to use snus was also observed.

3.4 Metabolic Effects

There were no adverse events (AEs) related to metabolic effects reported with the use of ZYN in any of the clinical studies conducted for this PMTA (Section 5.3).

A systematic literature review was conducted on the metabolic effects of snus use, including insulin resistance and type 2 diabetes, metabolic syndrome, and body weight (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.5 and Section 3.6).

Insulin Resistance

Based on the available literature, there was limited/suggestive evidence of no association between snus use and insulin resistance and glucose intolerance (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.5.1.1).

Type 2 Diabetes

Based on the available literature, there is balanced/mixed evidence for whether an association exists between snus use and type 2 diabetes (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.5.1.2). In addition, there was no difference in the prevalence of diabetes associated with snus use compared with smoking (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.6.1).

Metabolic Syndrome

Based on the available literature, there is limited/suggestive evidence of no association between snus use and metabolic syndrome (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.5.2 and Section 3.6.2).

Body Weight

Body weight issues with snus use were also examined in the literature and results were as follows (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.5.3):

- There was limited/suggestive evidence of no association between snus use and body mass index.
- There was inadequate/insufficient evidence to determine whether an association exists between snus use and being or becoming underweight.
- There was balanced/mixed evidence for an association between snus use and larger waist circumference or waist-to-hip ratio.
- There was inadequate/insufficient evidence to determine whether an association exists between snus use and incident weight gain.

3.5 Gastrointestinal Effects

GI effects including heart burn, gastroesophageal reflux symptoms, peptic ulcer, Crohn's disease, ulcerative colitis, irritable bowel syndrome, celiac disease, and other GI symptoms were reviewed as part of the systematic review of the literature on the health effects of snus. There were few articles identified, and the majority provided inadequate/insufficient evidence to determine an association (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.6).

3.6 Other Health Effects

Other health conditions, such as respiratory, musculoskeletal, and psychiatric disorders, were also reviewed as part of the systematic review of the literature on the health effects of snus. However, there were few articles identified, and the majority provided inadequate/insufficient evidence to determine an association (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.7).

3.7 All-Cause Mortality

Overall, the available literature studies currently provide limited/suggestive evidence of an association between snus use and all-cause mortality (Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.8.3). The current evidence reviewed in the evaluation of the literature suggested an approximately 30% decreased risk of all-cause mortality in snus users compared to smokers (Section I.1 Health Effects and Meta-Analysis Update Report, Section 3.7).

3.8 Pregnancy Outcomes and Reproductive Effects

Nicotine-containing products should not be used by pregnant or lactating women. A review of the literature on snus and pregnancy outcomes and reproductive effects can be found in Section I.1 Health Effects and Meta-Analysis Update Report, Section 2.7. There was limited/suggested evidence of an association found regarding the absolute risk of Swedish snus and stillbirth, preterm birth, lower birthweight, neonatal apnea, and small for gestational age. However, there was limited/suggestive evidence of no association found for early neonatal mortaility, maternal antenatal bleeding, maternal preeclampsia, and maternal gestational hypertension.

3.9 Health Risks of Dual Use and Switchers Compared to Smoking

Section I.1 Health Effects and Meta-Analysis Update Report, Section 4 summarizes results of the literature search and analyses of the following outcomes: oral and pharyngeal cancer, oral cancer, esophageal cancer and subtypes, pancreatic cancer, stomach cancer and subtypes, lung cancer, overall CVD, incident and fatal IHD and MI, nonfatal MI, incident and fatal stroke, sudden cardiac death, metabolic syndrome, diabetes prevalence and incidence, acute myeloid leukemia, and total mortality-related outcomes. Details can be found in the report; an overall summary is provided below.

The majority of endpoints had non-significant results for the comparison of dual users to never tobacco or never snus/smoke. There was mixed, non-significant evidence and/or no evidence of statistical interaction of health risks in dual users compared to smokers. Despite the potential limitations of the studies of dual users of snus and cigarettes, the evidence from several different cohorts suggests that dual users do not face a higher disease risk than do exclusive smokers and that, generally, the health risks among dual users appear to be similar to those observed among exclusive smokers.

Similarly, studies of switchers (ie, switched from cigarette use to snus use) provide some evidence for increased risk compared to never tobacco users; however, all studies provide evidence of decreased or non-significant risks in switchers compared to smokers. In this current review, the health risks among those who switch to snus from cigarettes were lower than those observed among individuals who continued to smoke cigarettes, and were generally comparable

to, or had lower point estimates than, the risk estimates observed among those who quit tobacco entirely.

4 SUMMARIES OF CLINICAL AND CONSUMER RESEARCH STUDIES CONDUCTED IN SUPPORT OF THE PMTA

The clinical development program was designed in compliance with the FDA draft guidance for industry entitled *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems*, dated May 2016.

A total of four clinical and two consumer research studies were conducted in support of the PMTA for ZYN:

- Three clinical pharmacology studies (SM 17-01, SM 17-03, and SM 18-01) that included the General Snus product sold in the US as a reference product
- One oral safety clinical study (SM 17-02)
- One likelihood of use consumer research study ((b) (4))
- One patterns of use consumer research study ((b) (4)) that enrolled ZYN users and non-users

The four clinical studies were conducted in Sweden, and the two consumer research studies were conducted in the US. A listing of these studies is provided in Table 2. Summaries of all six studies are provided in subsections below.

Table 2 Listing of Clinical and Consumer Research Studies Conducted with ZYN for this PMTA

Type of Study	Study No. (ISRCTN No.)	Study Design and Type of Control	Investigational Product(s); Administration Regimen	Number of Subjects	Population	Location of Study Report
In vivo, nicotine extraction, PD, safety	SM 17-01 (ISRCTN (b) (4))	Open-label, randomized, 14-way cross-over, single-dose administration	Test products: ZYN Smooth 3 mg - 15 min ZYN Smooth 3 mg - 60 min ZYN Smooth 6 mg - 15 min ZYN Smooth 6 mg - 60 min ZYN Smooth 3 mg (AMP[a]) - 15 min ZYN Smooth 3 mg (AMP[a]) - 60 min ZYN Smooth 6 mg (AMP[a]) - 15 min ZYN Smooth 6 mg (AMP[a]) - 60 min ZYN Wintergreen 3 mg (nicotine analysis) - 60 min ZYN Wintergreen 3 mg (flavor analysis) - 60 min ZYN Peppermint 3 mg (nicotine and flavor analysis) - 60 min ZYN Spearmint 3 mg (nicotine and flavor analysis) - 60 min Reference products: Swedish portion snus – General PSWL 1.0 g (8 mg nicotine) - 15 min Swedish portion snus – General PSWL 1.0 g (8 mg nicotine) - 60 min	Planned: 20 Enrolled: 20 Completed: 18	Healthy subjects aged ≥19 years who used tobacco-based snus for ≥1 year	Section H.3.1.2.1 Report Body
Nicotine PK, *in vivo* nicotine extraction, PD, safety	SM 17-03 (ISRCTN (b) (4))	Open-label, randomized, 5-way cross-over, single-dose administration	Test products: ZYN Smooth 3 mg ZYN Smooth 6 mg ZYN Smooth 3 mg (AMP[a]) ZYN Smooth 6 mg (AMP[a]) Reference product: Swedish portion snus – General PSWL 1.0 g (8 mg nicotine)	Planned: 18 Enrolled: 18 Completed: 17	Healthy subjects aged ≥19 years who used tobacco-based snus for ≥1 year	Section H.3.1.2.2 Report Body

Type of Study	Study No. (ISRCTN No.)	Study Design and Type of Control	Investigational Product(s); Administration Regimen	Number of Subjects	Population	Location of Study Report
Nicotine PK, *in vivo* nicotine extraction, safety	SM 18-01 (ISRCTN (b) (4))	Open-label, randomized, 7-way cross-over, single-dose administration	Test products: ZYN Smooth 6 mg ZYN Smooth 8 mg ZYN Wintergreen 6 mg ZYN Smooth 6 mg (lower lip) Reference products: Swedish portion snus – General PSWL (two pouches × 8 mg nicotine) American moist snuff, Longhorn Pouch Natural 18 mg (12 mg nicotine) American moist snuff, Longhorn Pouch Wintergreen 18 mg (12 mg nicotine)	Planned: 36 Enrolled: 36 Completed: 32	Healthy subjects aged ≥19 years who used tobacco-based snus for ≥1 year	Section H.3.1.2.3 Report Body
Oral safety	SM 17-02 (ISRCTN (b) (4))	Part 1: Open-label, randomized, 4-way cross-over, single-dose administration Part 2: Open-label, observational, follow-up for 6 weeks	Part 1: ZYN Smooth 3 mg ZYN Peppermint 3 mg 10% sucrose 10% xylitol Part 2: *Ad libitum* use of choice of ZYN: ZYN Smooth 3 mg ZYN Smooth 6 mg ZYN Cinnamon 3 mg ZYN Cinnamon 6 mg ZYN Peppermint 3 mg ZYN Peppermint 6 mg	Planned: 20 Enrolled: 20 Completed: 18 Planned: 60 Enrolled: 59 Completed: 57	Healthy subjects aged ≥19 years who used tobacco-based snus for ≥1 year and normal stimulated salivary secretion rate (≥0.7 mL/min)	Section H.3.1.3.1 Report Body

Type of Study	Study No. (ISRCTN No.)	Study Design and Type of Control	Investigational Product(s); Administration Regimen	Number of Subjects	Population	Location of Study Report
Consumer research (Likelihood of Use)	(b) (4)	Observational Pre-/post-exposure, repeated measures design Web-based survey of invited consumers	No product used	(b) (4)	(b) (4)	Section H.3.1.1.2 Report Body

Type of Study	Study No. (ISRCTN No.)	Study Design and Type of Control	Investigational Product(s); Administration Regimen	Number of Subjects	Population	Location of Study Report
Consumer research (Patterns of Use)	(b) (4)	2 phases: Retrospective – cross-sectional design to measure recalled TNP usage among ZYN users and non-users Prospective – longitudinal (10-week) evaluation of TNP patterns of use among ZYN users and non-users (subset of retrospective study participants)	None	(b) (4)	(b) (4)	Section H.3.1.1.1 Report Body

AMP=alternative manufacturing process (b) (4) ISRCTN=International Standard Randomized Controlled Trials Number; min=minutes; No.=number; PD=pharmacodynamics; PK=pharmacokinetics; PMTA=Premarket Tobacco Product Application; PSWL=portion snus white large; TNP=tobacco/nicotine product.

[a] The study evaluated the process effect, if any, between the manual process and the alternative process (b) (4) employed by Swedish Match.

4.1 Study SM 17-01

4.1.1 Study Design and Methods

Study SM 17-01 was an open-label, randomized, 14-way cross-over, single-dose study designed to evaluate the *in vivo* extraction of nicotine and flavor compounds from ZYN compared with conventional, tobacco-based snus (General portion snus white large [PSWL], which received PMTA marketing authorization on 10 November 2015 and modified risk order on 22 October 2019) in healthy, current daily snus users (Section H.3.1.2.1 Report Body). The primary objective was to compare the estimated *in vivo* extracted dose of nicotine from ZYN containing 3 and 6 mg of nicotine, respectively, with that from General PSWL 1.0 g containing 8 mg of nicotine. Secondary objectives were as follows:

- To assess pulse rate as a surrogate endpoint for systemic uptake of nicotine
- To compare each subject's rating of subjective effect ("head buzz") and pulse rate
- To estimate the *in vivo* extracted dose of flavor components to assess the overall flavor exposure from ZYN
- To assess AEs

Twenty healthy subjects aged ≥19 years who used tobacco-based snus ≥1 year with a weekly consumption rate of three or more snus cans (brands with nicotine content <1%) or two or more cans (brands with nicotine content >1%) were enrolled and randomized to one of four treatment sequences (n=5 per sequence) using a Latin Squares approach (Section H.3.1.2.1 Report Body, Table 9.4-1). The reference products were General PSWL 1.0 g (8 mg nicotine) at 15-minute and 60-minute administrations. The test products were as follows:

- ZYN Smooth containing 3 mg nicotine per portion - 15-minute administration
- ZYN Smooth containing 3 mg nicotine per portion - 60-minute administration
- ZYN Smooth containing 6 mg nicotine per portion - 15-minute administration
- ZYN Smooth containing 6 mg nicotine per portion - 60-minute administration
- ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process) - 15-minute administration
- ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process) - 60-minute administration
- ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process) - 15-minute administration
- ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process) - 60-minute administration

- ZYN Wintergreen containing 3 mg nicotine per portion (nicotine analysis) - 60-minute administration
- ZYN Wintergreen containing 3 mg nicotine per portion (flavor analysis) - 60-minute administration
- ZYN Peppermint containing 3 mg nicotine per portion (nicotine and flavor analysis) - 60-minute administration
- ZYN Spearmint containing 3 mg nicotine per portion (nicotine and flavor analysis) - 60-minute administration

ZYN Smooth was tested at two nicotine strengths, two administration times, and two different manufacturing production techniques (b) (4) [redacted] this study evaluated whether there was process effect as an additional objective.

Subjects visited the clinic on separate days (Visit 2 to Visit 16) for the 14 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 according to the randomized treatment sequence. The subjects kept the pouch still between the upper lip and the gum for 15 or 60 minutes and were instructed not to manipulate the pouch with the tongue or lips. The subjects were instructed not to eat or drink from 30 minutes before and during dose administration.

Each used pouch was collected and frozen (-20°C) pending analyses of nicotine and flavor components. Unused pouches were collected and frozen (-20°C) pending analysis and served as references in the calculations of extracted doses.

Assessments were as follows:

- The extracted amount of nicotine was calculated by using the average reference concentration of nicotine by weight from 10 unused portions and multiplying this value with the individual measured weight of each pouch used in the study. From this value, the remaining used pouch nicotine content was subtracted to get a value for the extracted amount of nicotine.
- Pulse rate was measured at the following time points: before (0) and at 5, 10, 15, 30, and 60 minutes after each dose.
- The subject's subjective rating of product "strength" using a visual analog scale (VAS) (head "buzz," "head rush," "hit," feeling alert, overall "product strength"), anchored with "not at all" to "extremely," was recorded. VAS scores were obtained at the following time points: before (0) and 5, 10, 15, 30, and 60 minutes after each product was administered.

- AEs and serious adverse events (SAEs) were collected starting from the start of IP administration until the last follow-up visit.

4.1.2 Results and Conclusions

A total of 20 white subjects were randomized in this study. Half of the subjects were female, and the mean (standard deviation [SD]) age was 28.8 (8.83) years. Mean (SD) pulse was 67.5 (9.77) beats per minute (bpm) at screening.

All 20 randomized subjects were included in the full analysis set (FAS). Two subjects in treatment sequence C withdrew consent after Visit 3 and received one single dose of ZYN Smooth 3 mg (60 minutes) and one single dose of ZYN Smooth 6 mg (15 minutes). Eighteen subjects completed the study (received all treatments) and were included in the per-protocol analysis set (PPS).

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

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

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

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

The results of head buzz (measured by VAS) were not conclusive. There were no statistically significant differences in the change in head buzz between the test products and the reference product at the majority of time points during the 15-minute administration. Head buzz changed over time to a similar extent in all treatment groups. After the 60-minute administration, the increase was significantly larger for the reference product compared to ZYN 3 mg and compared to the flavored ZYN products. No significant difference in head buzz was observed between flavors or production techniques.

The mean (SD) extracted doses of flavors from ZYN Wintergreen 3 mg, ZYN Peppermint 3 mg, and ZYN Spearmint 3 mg, respectively, were (b) (4) mg (b) (4) (ZYN Wintergreen 3 mg), (b) (4) mg (b) (4) and (b) (4) mg (b) (4), respectively (ZYN Peppermint 3 mg), and (b) (4) mg (b) (4) and (b) (4) mg (b) (4), respectively (ZYN Spearmint 3 mg).

Administration of single doses of ZYN was well tolerated by the healthy subjects, and no safety concerns were observed in this study. A total of 54 AEs were reported by 10 subjects during the study, and 36 AEs were judged to have a possible or probable relationship to treatment. The number of subjects reporting related AEs ranged from one to five during 11 of the 14 different treatments. Occasional AEs, mainly GI disorders, were reported. There were no deaths, other SAEs, or discontinuations due to AEs during the study.

4.2 Study SM 17-03

4.2.1 Study Design and Methods

Study SM 17-03 was an open-label, randomized, five-way cross-over, single-dose study to assess nicotine PK and subjective effects of a single dose of a ZYN compared with conventional, tobacco-based snus (General PSWL) among current healthy daily snus users (Section H.3.1.2.2 Report Body). The primary objective was 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 a single dose of ZYN containing 3 and 6 mg of nicotine to that of a single dose of General PSWL 1.0 g (8 mg nicotine). Secondary objectives were as follows:

- To compare area under the plasma concentration-time curve from time zero to 60 minutes (AUC_{60min}), maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the plasma concentration-time curve from time zero to last observation ($AUC_{0\text{-}last}$), and terminal half-life ($t_{½}$ [z]) of ZYN to General PSWL.

- To compare the estimated *in vivo* extracted amount of nicotine from ZYN containing 3 and 6 mg of nicotine, respectively, with General PSWL containing 8 mg of nicotine.

- To compare pulse rate and subjective effects ("head buzz") after study product administration (as a proxy for *in vivo* nicotine uptake)

- To collect AEs

Eighteen healthy subjects aged ≥19 years who had used tobacco-based snus for ≥1 year with a weekly consumption rate of three or more snus cans (for brands with nicotine content ≤1%) or two or more cans (for brands with nicotine content >1%) were enrolled and randomized to one of four treatment sequences using a Latin Squares approach (Section H.3.1.2.2 Report Body, Table 9.4-1). The reference product was General PSWL 1.0 g (8 mg nicotine). The test products were as follows:

- ZYN Smooth containing 3 mg nicotine per portion

- ZYN Smooth containing 6 mg nicotine per portion

- ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process)

- ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process)

ZYN Smooth was tested at two nicotine strengths and two different manufacturing production techniques (b) (4)

(b) (4) this study evaluated whether there was process effect as an additional objective.

Subjects visited the clinic on separate days (Visit 2 to 6) for the five 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 IPs were administered as single doses according to the randomized treatment sequence. The subjects kept the pouch still between the upper lip and the gum for 60 minutes 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 minutes before application of treatment, during application of IPs, and 30 minutes after the IP had been taken out. Each used pouch was collected and frozen (-20°C) pending analyses of nicotine.

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

Assessments were as follows:

- Nicotine plasma concentrations were determined at the following time points: before (0) and at 5, 10, 15, 30, and 60 minutes, and 1.5, 2, 4, and 6 hours after administration of each IP.
- Pulse rate was measured at the following time points: before (0) and at 5, 10, 15, 30, and 60 minutes after administration of each IP.
- Each subject's rating of product "strength" using a VAS (head "buzz," "head rush," "hit," feeling alert, overall "product strength"), anchored with "not at all" to "extremely" was obtained before (0) and at 5, 10, 15, 30, and 60 minutes after administration of each product.
- AEs and SAEs were collected starting from the start of IP administration until the last follow-up visit.

4.2.2 Results and Conclusions

A total of 18 subjects were randomized in this study. The majority were white (94%) and male (83%), and the mean (SD) age was 36.6 (12.7) years. The mean (SD) pulse was 69.7 (8.01) bpm at screening.

Seventeen of the 18 subjects completed the study. One subject in treatment sequence C withdrew consent after Visit 2 and received only one dose of IP (ZYN Smooth 6 mg [alternative manufacturing process]). Eighteen subjects were included in the FAS, and 17 subjects were included in the PPS. Since the PPS comprised 17 of 18 subjects, all analyses were performed using the PPS.

There were statistically significant differences in mean AUC_{inf} between each of the four test products and the reference product (General PSWL 1.0 g [8 mg]). The AUC_{inf} of the ZYN 3 mg products was significantly lower compared to that of the reference product, and the AUC_{inf} of the ZYN 6 mg products was significantly higher.

The extracted amount of nicotine from ZYN 3 mg products (both manufacturing processes) was significantly lower compared to that of the reference product. The extracted amount from ZYN 6 mg products (both manufacturing processes) was significantly higher compared to the reference product.

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

For the PK parameters, there were statistically significant differences in $AUC_{0\text{-last}}$, $AUC_{60\text{min}}$, and C_{max} between each of the test products and the reference product, whereas no statistically significant differences were seen in terms of $t_{½}$ (z) and t_{max}.

There were no statistically significant differences in AUC_{inf} between the manufacturing production techniques for either ZYN dose (3 or 6 mg).

There were no statistically significant differences in the change in pulse rate between any of the test products and the reference product at any 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 bpm.

There were statistically significant differences in head buzz between each of the test products and the reference product at a majority of the 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.

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, General PSWL 1.0 g (8 mg) (reference) 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 reference group. Interestingly, the increase in head buzz was statistically significantly smaller in the ZYN 6 mg group compared to the reference group.

Conventional, General PSWL 1.0 g (8 mg) (reference) 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 reference group compared to the ZYN 3 mg group but was associated with a larger increase in head buzz in the reference group.

Administration of single doses of ZYN was well tolerated by the healthy subjects, and no safety concerns were observed in this study. A total of 16 AEs were reported by eight subjects during the study, and two AEs (dry mouth) were judged to have a possible or probable relationship to treatment. There were no deaths, other SAEs, discontinuations due to AEs during the study.

4.3 Study SM 18-01

4.3.1 Study Design and Methods

Study SM 18-01 was an open-label, randomized, seven-way cross-over, single-dose study to assess nicotine plasma concentrations and PK of a single dose of ZYN compared with conventional, tobacco-based snus (General PSWL) and American moist snuff (Longhorn Pouch) among current, healthy daily snus users (Section H.3.1.2.3 Report Body). The primary objective was to evaluate each subject's nicotine plasma concentrations of nicotine after administration of a single dose of ZYN Smooth 6 mg compared to a single dose of two pouches of General PSWL (2 × 8 mg nicotine). Secondary objectives were to:

- Compare t_{max}, C_{max}, AUC_{inf}, and $AUC_{0\text{-}last}$ from each dose of ZYN Smooth pouches, General PSWL pouches, and American moist snuff pouches
- Assess the effect of the flavor component (methyl salicylate) on nicotine plasma concentrations for ZYN Wintergreen and American moist snuff Wintergreen pouches, respectively
- Assess if there was a difference in nicotine plasma concentrations between upper lip and lower lip placement of ZYN Smooth
- Compare the estimated *in vivo* extracted amount and rate of extraction of nicotine from each dose
- Assess plasma levels of salicylate for the treatments with pouches containing Wintergreen flavor
- Compare AEs from each dose

Thirty-six healthy subjects aged ≥19 years who had used tobacco-based snus for ≥1 year with a weekly consumption rate of two or more snus cans (preferably brands with nicotine content ≥1%) were enrolled and randomized to one of four treatment sequences (n=9 per sequence) (Section H.3.1.2.3 Report Body, Table 9.4-1). The four test and three reference products were as follows:

- Test products:
  - ZYN Smooth 6 mg
  - ZYN Smooth 8 mg
  - ZYN Wintergreen 6 mg
  - ZYN Smooth 6 mg lower lip

- Reference products:

  – General PSWL, two pouches x 8 mg nicotine (hereafter referred to as General PSWL [2 × 8 mg])

  – American moist snuff, Longhorn Pouch Natural 18 mg (hereafter referred to as Longhorn Natural 18 mg)

  – American moist snuff, Longhorn Pouch Wintergreen 18 mg (hereafter referred to as Longhorn Wintergreen 18 mg)

These reference products were chosen based on the fact that many brands of smokeless tobacco on the US market have a nicotine content that is higher, or even substantially higher (range: 5 to 20 mg per pouch)than the 8 mg/pouch snus product used in Study SM 17-03. Also, more than 10% of all snus users frequently use two or more pouches simultaneous, and consumers of loose products use larger portion size, average 2.6 g, resulting in a three-fold higher daily consumption compared to consumers of pouch products (Digard et al 2009).

Subjects reported to the clinic on separate days for the seven experimental sessions, with a minimum washout period of 24 hours between sessions. The subjects were instructed to abstain from snus or other nicotine delivery products from 8:00 p.m. the evening before (minimum abstinence period: 13 hours, maximum abstinence period: 13.5 hours) and to refrain from smoking 24 hours before each experimental session. All sessions were performed during the morning hours to facilitate abstinence. The subjects certified abstinence before each treatment was started.

The treatments were administered as single doses in a pre-determined randomized order. The subject kept the pouch(es) still between the upper lip (lower lip for treatment 4) and the gum for 60 minutes 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 minutes before the application of treatment, during the application of IPs, and 30 minutes after the IP had been taken out. After 60 minutes, the pouches were collected and frozen (-20°C) pending analyses of nicotine. Blood samples for assessment of the plasma levels of nicotine and salicylate were collected at pre-defined time points from pre-dose to 6 hours after IP administration.

A telephone follow-up (Visit 9) was conducted one week after the last dose.

Assessments were as follows:

- Nicotine plasma concentrations were determined at pre-set time points: before (0) and at 5, 10, 15, 30, 60, 90, 120, 240, and 360 minutes after administration of each IP.

- AEs and SAEs were collected starting from the start of IP administration until the last follow-up visit.

4.3.2 Results and Conclusions

A total of 36 white subjects were randomized in this study. The majority were male (64%), and the mean (SD) age was 33.9 (14.7) years.

All 36 randomized subjects were included in the FAS. Four subjects were withdrawn (two subjects due to being lost to follow-up and two subjects due to non-compliance), and 32 subjects completed the study. A total of 30 subjects were included in the PPS; those excluded were excluded due to being lost to follow-up (two subjects), being unable to draw blood on visit (one subject), non-compliance (two subjects), and nausea (one subject).

Since it was discovered that the intended ZYN 6 mg pouches only contained approximately 4.5 mg nicotine, the PK and extraction data were not included in the analyses, and the conclusions are based on the comparison between the ZYN 8 mg product and General PSWL 2 × 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg. The study demonstrated that ZYN Smooth 8 mg did not entail higher nicotine uptake than General PSWL 2 × 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg, which represent commercially available tobacco-based snus and snus-like products that are currently common on the Scandinavian and US markets.

The mean AUC_{inf} of General PSWL 2 × 8 mg was significantly higher than the mean AUC_{inf} of ZYN Smooth 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg, respectively.

Corresponding results were observed for the extracted dose of nicotine, ie, the mean extracted dose of nicotine from General PSWL 2 × 8 mg was significantly higher than the mean extracted dose from ZYN Smooth 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg, respectively. In addition, the mean extracted dose of nicotine from ZYN Smooth 8 mg was significantly higher than the mean amount extracted from Longhorn Natural 18 mg, although the uptake was not higher. For all products but General PSWL 2 × 8 mg, there was a strong correlation between the AUC_{inf} and the extracted amount of nicotine.

The mean nicotine rate of extraction from ZYN Smooth 8 mg was significantly higher than the rate of extraction from General PSWL 2 × 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg. In addition, the rate of extraction of nicotine from General PSWL 2 × 8 mg was significantly higher than the rate of extraction from Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg.

The mean $AUC_{0\text{-}last}$ and mean C_{max} of General PSWL 2 × 8 mg were significantly higher than the mean $AUC_{0\text{-}last}$ and mean C_{max} of ZYN Smooth 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg, respectively.

The mean t_{max} and mean $t_{½\ (z)}$ of ZYN Smooth 8 mg were significantly shorter than the mean t_{max} and mean $t_{½\ (z)}$ of Longhorn Wintergreen 18 mg. For baseline-adjusted data, the mean t_{max} of ZYN Smooth 8 mg was also significantly shorter than the mean t_{max} of General PSWL 2 × 8 mg.

There were no statistically significant differences in mean AUC_{inf}, $AUC_{0\text{-}last}$, mean $C_{max,}$ or extracted dose of nicotine between ZYN Smooth 8 mg and either Longhorn Natural 18 mg or Longhorn Wintergreen 18 mg or between Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg. In addition, there were no statistically significant differences in the rate of extraction between Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg or in t_{max} between most of the IPs.

Administration of single doses of nicotine-containing products was safe and well tolerated by the healthy subjects in this study. Ten subjects (28%) reported a total of 18 AEs during the 24 hours following each administration of ZYN Smooth 8 mg, General PSWL 2 × 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg. There were no deaths, other SAEs, or

discontinuations due to AEs. All AEs were mild to moderate in intensity. The most common AE was nausea. Overall, the majority of the AEs were AEs that are usually associated with nicotine exposure.

4.4 Study SM 17-02

4.4.1 Study Design and Methods

Study SM 17-02 was a study of oral health associated with the use of ZYN among current daily snus users (Section H.3.1.3.1 Report Body). There were two parts to the study:

- Part 1 was an open-label, randomized, four-way cross-over, single administration (60 minutes) study in which subjects received the following:
  - ZYN Smooth 3 mg
  - ZYN Peppermint 3 mg
  - 10% sucrose
  - 10% xylitol
- Part 2 was an open-label, observational, six-week follow-up study during which subjects were encouraged to substitute as much as possible of their snus with *ad libitum* use of the ZYN of their choice (Smooth 3 or 6 mg, Peppermint 3 or 6 mg, or Cinnamon 3 or 6 mg). Use of ZYN, snus, or any other nicotine delivery product was monitored based on self-reports. Clinical visits were scheduled every two weeks. At each visit, data were collected on product use since last visit, AEs, plaque acidogenicity, oral microflora, plaque amount, and oral lesions. Clinical photos were taken to facilitate comparisons. "Snus lesions" at the site where participants typically place their snus/ZYN pouch were assessed using a four-degree scale as proposed by Axell et al 1976. At each visit, the subject reported any local or general adverse symptoms.

The primary objectives of each part of the study were as follows:

- Part 1: Assessment of dental plaque acidogenicity after short-term exposure (60 minutes) to study products (a flavored and an unflavored ZYN pouch), 10% sucrose (positive control), and 10% xylitol (negative control)
- Part 2: Assessment of dental plaque acidogenicity during a total of six weeks of *ad libitum* use of ZYN

The secondary objectives of each part of the study were to evaluate the clinical tolerability and safety of ZYN with respect to effects on the oral mucosa as measured by the following:

- Part 1: AEs
- Part 2: AEs, changes in the oral microflora compared to screening, and the appearance and number of oral mucosal lesions (including presence and grade of "snus lesions" at the site where the pouches typically are placed by the consumer) compared to screening

Healthy subjects aged ≥19 years who had used tobacco-based snus ≥1 year with a weekly consumption of three or more snus cans (for brands with nicotine content ≤1%) or two or more cans (for brands with nicotine content >1%) and had a normal stimulated salivary secretion rate (≥0.7 mL/min) were eligible to participate. Subjects from Part 1 were eligible to participate in Part 2 after undergoing a new screening visit.

The subjects in both parts of the study refrained from approximal tooth cleaning for 72 hours, toothbrushing for 48 hours, and eating or drinking for two hours prior to each visit.

4.4.2 Results and Conclusions

Overall, the study showed that ZYN products did not adversely affect dental plaque acidogenicity after single-dose administration in healthy snus users, and that ZYN was safe and well tolerated by the subjects.

Part 1

Of the 20 subjects enrolled in Part 1, all were white (non-Hispanic), and the majority were male (70%). The mean (SD) age was 34.6 (11.1) years, and all had a normal stimulated salivary secretion rate (mean [SD]=2.3 [1.5] mL/minute).

In Part 1, 20 subjects were included in the FAS. Two subjects were withdrawn (due to severe non-compliance and withdrawal of consent, respectively), and 18 subjects completed the study and were included in the PPS.

After single-dose administration of IP in Part 1, administration of 10% sucrose solution (positive control) resulted in a drop in plaque pH caused by the production of organic acids by bacterial fermentation of sucrose (Figure 6). Only for sucrose were pH values low enough to increase the risk for demineralization of dentin (pH <6.2) and enamel (pH <5.5). In contrast, after administration of a 10% xylitol solution (negative control), the plaque pH remained essentially unchanged compared to before administration. During administration of ZYN Smooth 3 mg and ZYN Peppermint 3 mg, the plaque pH value was slightly higher (approximately 0.2 units) compared to the pre-administration value. There were no statistically significant differences between the two ZYN products. The results show that single-dose administrations of the two ZYN products do not promote plaque acidogenesis.

A total of two AEs were reported by one subject during Part 1; both were mild in intensity and assessed as unrelated by the investigator. There were no deaths, other SAEs, or discontinuations due to AEs.

Part 2

Of the 59 subjects enrolled in Part 2, all were white (non-Hispanic), and the majority were male (66%). The mean (SD) age was 31.4 (10.1) years, and all had a normal stimulated salivary secretion rate (mean [SD]=2.3 [1.0] mL/minute).

In Part 2, 59 subjects were included in the FAS. Two subjects were withdrawn due to withdrawal of consent, and 57 subjects completed the study. A total of 56 subjects were included in the PPS; two subjects were excluded for withdrawal of consent and one subject was excluded due to being wrongly enrolled (ie, subject was on hypertension medication, which was an excluded medication).

Dental plaque acidogenicity was evaluated by measuring the plaque pH before and up to 60 minutes after rinsing the mouth with a 10% sucrose solution. Acidogenicity was determined at the Screening visit and after 2, 4, and 6 weeks (Visits 3 to 5) of *ad libitum* administration of ZYN pouches. The pH drop caused by exposure to sucrose (ie, the acidogenicity) was largest at the Screening visit and became progressively smaller during the time of the study (Figure 7). The largest negative change in pH value was significantly larger at the Screening visit compared to at the visits during the study. Furthermore, the areas under the plasma concentration-time curve (AUCs) below pH 6.2 and pH 5.5 were significantly larger at the Screening visit than at the visits during the study. The results show that acidogenicity was decreased during the study compared to at the Screening visit.

For the majority of assessments of plaque amount, there were no statistically significant changes for the subjects during Part 2.

The number of *Streptococcus mutans* (*S. mutans*) at four and six weeks was significantly higher compared to baseline. The differences were seen for all subjects and for the female subjects, but not for the male subjects. However, it is worth noting that at baseline, the observed number of *S. mutans* were considerably lower for the female subgroup compared to the male subgroup. There were no statistically significant changes from baseline for Lactobacilli during Part 2.

The number of subjects with no lesions increased from 9% at screening to 30% at six weeks. The degree of lesions in the mucosa at placement of the pouch was significantly lower at two, four, and six weeks compared to baseline, and the number of subjects with lesions decreased from 90% to 70%. There was a statistically significant correlation between change in oral mucosal lesions and percentage of ZYN products used for all visits except for the female subjects at four weeks. There was no indication of changes in the incidence of gingival retraction during the study; it varied between 54% and 57% during the study.

A total of 10 AEs were reported by nine subjects during Part 2. There were no deaths, other SAEs, or discontinuations due to AEs. The majority of AEs were of mild intensity, and the rest were of moderate intensity. Half of the AEs were assessed by the investigator as unrelated to treatment with IP.

4.5 Consumer Research Study (b) (4) (Likelihood of Use)

4.5.1 Study Design, Methods, and Main Findings

Study (b) (4) was an observational study with a pre- and post-exposure design to assess the likelihood of ZYN use (Section H.3.1.1.2 Report Body).

Study findings did not support that marketing of ZYN would have an adverse impact on public health. In fact, data suggest that ZYN could have a positive effect on public health. This conclusion was motivated mainly by results showing the following:

1. Respondents not currently using tobacco/nicotine products (TNPs) were unlikely to initiate/reinitiate use of TNPs after being exposed to the tested ZYN stimuli.
2. Current tobacco users including current cigarette smokers demonstrated interest in purchasing ZYN (and could thus potentially benefit from a complete switch from cigarettes to ZYN).
3. Exposure to the ZYN stimuli did not affect intention to quit among TNP users.

The study population (b) (4) consisted of US residents of legal age for TNP use per local requirements. Respondents were enrolled from one of seven cohorts based on self-reported current TNP use (see Section H.3.1.1.2 Report Body, Table 1 for detailed definitions of each cohort):

1. Never tobacco users from legal age to 24 years of age
2. Never tobacco users >24 years of age
3. Former tobacco users from legal age and older
4. Current cigarette smokers with intention to quit from legal age to 24 years of age
5. Current cigarette smokers with intention to quit >24 years of age
6. Current cigarette smokers without intention to quit from legal age and older
7. Current tobacco users (excluding cigarettes) from legal age and older

The definition of TNP use and the product types constituting TNP for this study were adapted from the Population Assessment of Tobacco and Health (PATH) study (USDHHS 2017). By establishing separate cohorts, efforts were made to oversample people who use TNP of legal age to 24 years of age as well as TNP users with intention to quit.

Respondents were given study stimuli consisting of a one-page ZYN description and packaging label for ZYN Cool Mint 3 mg that indicated product information, including instructions for use, strengths, number of pouches in a canister, and flavors, as well as the required warning label that nicotine is an addictive chemical. Data for the study were obtained using responses from a customized web-based survey of invited consumers who met inclusion and exclusion criteria (see Section H.3.1.1.2 Report Body, Section 9.2) and provided informed consent to participate in the study. The study sample utilized a screening framework based on socio-demographic characteristics of the adult population from the PATH study (USDHHS 2017). The overall

recruitment methodology was expected to provide socio-demographic profiles consistent with the adult population based on PATH study data for each of the study cohorts. Cognitive interviews informed the survey design to ensure that the survey materials were appropriate and sufficiently clear to respondents.

The two primary objectives of this study were as follows:

1. Among all respondents, assess whether being exposed to ZYN stimuli had an impact on perceptions and intentions related to the use of TNP

- Among TNP never-users legal age to 24 years, TNP never-users older than 24 years, and former TNP users, evaluate:
  - Current likelihood to initiate or reinitiate TNP based on intention to buy TNP; the term “initiate” is only pertinent to TNP never-users, ie, those not currently using TNP. Similarly, the term “reinitiate” is only pertinent to TNP former users
  - Future likelihood to initiate or reinitiate TNP based on intention to buy ZYN after being exposed to ZYN stimuli
- Among cigarette smokers with intention to quit, cigarette smokers without intention to quit, and current tobacco users (excluding cigarettes), evaluate:
  - Current use of TNP
  - Future intention to buy ZYN after being exposed to ZYN stimuli
  - Future intention to use current TNP after being exposed to ZYN stimuli
- Among cigarette smokers with intention to quit, cigarette smokers without intention to quit, and current tobacco users (excluding cigarettes), evaluate:
  - Current intention to quit use of TNP
  - Future intention to quit use of TNP after being exposed to ZYN stimuli

2. Among all respondents, measure the appeal of various ZYN brand and product attributes after being exposed to ZYN stimuli. Attributes included:

- Overall look and feel
- Variety of flavors
- Product design
- Physical product

- Child-safety lid

The two secondary objectives of this study were as follows:

1. Among all respondent cohorts, explore the variation in perceptions of absolute risk associated with never having used any TNP, smoking cigarettes, and using ZYN.

   - Measurement of absolute risk of non-usage and smoking prior to showing respondents the ZYN stimuli.

   - Measurement of absolute risk of ZYN to occur after showing respondents the ZYN stimuli.

   The health conditions under consideration when assessing absolute risk were adult tooth loss, gum disease, mouth cancer, and serious health problems.

2. Among all respondent cohorts, explore variation in perceptions of relative risk of using ZYN as opposed to:

   - Using other tobacco products;

   - Using aids to help stop smoking;

   - Quitting all TNP; and

   - Never using any TNP.

   All measurements of relative risk were collected after respondents were exposed to the ZYN stimuli. The health conditions under consideration when assessing relative risk were adult tooth loss, gum disease, mouth cancer, and serious health problems.

4.5.2 Results and Conclusions

This observational study included 5,165 respondents who met the study eligibility criteria from the seven cohorts described in Table 3.

Table 3 Definition and Final Sample Size of Each Cohort (Study (b) (4) [Likelihood of Use])

Cohort Number	Cohort Description	Final Sample Size (b) (4) n (%)
1	Never tobacco users from legal age to 24 years of age	(b) (4)
2	Never tobacco users > 24 years of age	
3	Former tobacco users from legal age and older	
4	Current cigarette smokers with intention to quit from legal age to 24 years of age	
5	Current cigarette smokers with intention to quit > 24 years of age	
6	Current cigarette smokers without intention to quit from legal age and older	

Cohort Number	Cohort Description	Final Sample Size (b) (4) n (%)
7	Current tobacco users (excluding cigarettes) from legal age and older	(b) (4)

Respondent mean age was (b) (4) years (range: 18 to 92 years) (Section H.3.1.1.2 Attachment 17.1 Descriptive Tables 1-14, Table 1b). (b) (4) (Section H.3.1.1.2 Attachment 17.1 Descriptive Tables 1-14, Table 1a). Respondent gender was similar in four of the seven cohorts, except for the never tobacco users, which had a majority of females, and current tobacco users from legal age and older, which had a majority of males (Section H.3.1.1.2 Report Body, Appendix 16.1, Table 11). (b) (4)

Study findings support the conclusion that overall, the introduction of ZYN does not appear to compromise public health in any way, based on likelihood of use and perceptions of risk as assessed in the current study. Specifically, results demonstrated that:

- Respondents who did not use TNPs were not likely to initiate or reinitiate TNPs after viewing the ZYN description and packaging label ("stimuli").
- Current tobacco users and current cigarette smokers demonstrated some interest in purchasing ZYN in the future. Additionally, cigarette smokers with intention to quit showed greater interest in purchasing ZYN than cigarette smokers without intention to quit.
- Among TNP users, exposure to the ZYN stimuli did not affect their intention to quit TNP, as reflected in Motivation to Stop Scale (MTSS) scores. However, according to future intention to use TNP, the majority of smokers with intention to quit did report that they would cut back or completely quit the use of cigarettes, moist snuff, cigars/cigarillos/filtered cigars filled with tobacco, and/or pipe tobacco after exposure to the ZYN stimuli.
- Respondents perceived that there are risks of certain health conditions associated with using ZYN, but those risks are 1) the same or lower than cigarettes, both cigarettes/ZYN, moist snuff, chewing tobacco, and snus; and 2) higher than using no TNP.

4.6 Consumer Research Study (b) (4) (Patterns of Use)

4.6.1 Study Design, Methods, and Main Findings

Study (b) (4) (Patterns of Use) was designed for a descriptive analysis of ZYN users' and ZYN non-users' patterns of use and perceptions of health risk in the absolute, relative to other TNP, and in combination with ZYN and consisted of two distinct phases (Section H.3.1.1.1 Report Body):

1. Retrospective Study, which utilized a cross-sectional design to measure recalled TNP usage among ZYN users and ZYN non-users

2. Prospective Study, which longitudinally evaluated TNP patterns of use among ZYN users and ZYN non-users over a 10-week observation period

Overall, study findings did not indicate that ZYN adversely affects public health. In fact, some results suggested a potential for beneficial effects. For instance, nearly all ZYN consumers had a history of prior tobacco use, and the proportion of ZYN users who also smoked cigarettes declined from 42.1% the weeks before initiating ZYN to 15.0% at the time of the survey. ZYN users who also smoked reported a greater intention to quit than non-ZYN users, and use of cigarettes and moist snuff trended downward among those who also used ZYN during a 10-week follow up period.

The study population consisted of the US residents of legal age for TNP use per local requirements. ZYN users and non-users were defined byself-reported TNP use, with the criterion that ZYN users were required to have entered the survey by way of an invitation sticker placed on the ZYN canister. ZYN non-users were recruited through online consumer survey panels. The definition of TNP use and the product types constituting TNP for this study were adapted from the PATH study (USDHHS 2017).

Respondents for the Retrospective Study (b) (4) were enrolled from two cohorts:

- ZYN users (b) (4)
  - All ZYN users were recruited through the canister sticker program. Since the number of ZYN users is small, an invitation sticker was placed directly on the ZYN canisters for all varieties of ZYN available at retail outlets from 27 November 2017 to 15 December 2017 to recruit ZYN users most efficiently. The sticker initiative targeted approximately 4,500 retail stores carrying ZYN across the 11 states (AZ, CA, CO, ID, MT, NM, NV, OR, UT, WA, and WY) where ZYN is sold.
  - Users were then confirmed through screening to use nicotine pouches fairly regularly and now use ZYN pouches every day or some days.
- ZYN non-users (b) (4) were TNP users that
  - Never used ZYN

  OR
  - Did not use ZYN regularly AND did not currently use ZYN every day or some days

  AND at least one of the following:
  - smoked 100 or more cigarettes during their lifetime AND currently smoke cigarettes every day or some days
  - were a regular user of any of the following products AND now use the product(s) every day or some days: e-cigarettes, cigars, cigarillos, filtered cigars, pipe filled with tobacco, hookah or water pipe filled with tobacco, smokeless tobacco (snus pouches, moist snuff, dip, or chewing tobacco)

For the Retrospective Study, ZYN users and non-users accessed a 10- to 20-minute retrospective survey where respondents were asked to self-report TNP use. Upon completion of the Retrospective Study survey, respondents were invited to participate in the Prospective Study. The Prospective Study survey instrument consisted of a daily survey and a biweekly survey. Only respondents who completed all 10 weeks in the Prospective Study period were included in the final analyses. A total of [redacted] respondents ([redacted] participated in the Prospective Study. Only respondents who completed all 10 weeks in the Prospective Study period were included in the final analyses.

A total of [redacted] respondents [redacted] participated in the Prospective Study. Objectives from the Prospective Study were included as secondary objectives since Swedish Match could not guarantee a specific sample size or composition from that study.

Primary objectives were based on data from the Retrospective Study and were as follows:

1. Comparison of TNP patterns of use between ZYN users and non-users over the past 30 days.

2. The study examined usage patterns among respondents and, in particular, examined how ZYN users utilize other TNP products compared with ZYN non-users. Of specific interest were usage patterns of cigarettes, smokeless tobacco, aids to help stop smoking, and ZYN itself.

3. Comparison among ZYN users of TNP patterns of use over the last 30 days with TNP patterns of use during the weeks prior to using ZYN.

4. Within the cohort of ZYN users, the study explored how usage of TNP changed from the period prior to starting ZYN to the last 30 days. Of particular interest was whether usage of ZYN offset usage of products such as cigarettes and smokeless tobacco.

5. Evaluation of the level of compliance among ZYN users with ZYN usage instruction over the last seven days.

6. Focused on the last seven days, the study explored how ZYN users reported using the product. Specifically of interest were compliance with usage instructions and presence/absence of product misuse.

Secondary objectives based on data from the Retrospective Study were as follows:

1. Assessment of perceptions of absolute risk of certain health conditions [redacted] among ZYN users and ZYN non-users.

   The study measured the perceived risk of the aforementioned health conditions attributed to using only ZYN daily, smoking only cigarettes daily, and never having used any TNP.

2. Assessment of ZYN users' perceptions of the relative risk of certain health conditions (b) (4) associated with ZYN compared with using other TNP, aids that help stop smoking, and never having used any TNP.

   The study measured the perceived risk of the aforementioned health conditions attributed to using only ZYN daily relative to using only other TNP daily, daily use of aids to help stop smoking, or never having used any TNP.

3. Assessment of ZYN users' perceptions of the relative risk of certain health conditions (b) (4) associated with adding ZYN use to existing TNP use.

   The study measured the perceived relative risk of the aforementioned health conditions attributed to using both ZYN and other TNP compared with using other TNP alone. From there, further analysis delved into how adding ZYN to existing TNP use alters perceived risk.

4. Assessment of ZYN users' perceptions of relative risk of certain health conditions (b) (4) to a person who quits use of all TNP compared with a person who quits all TNP except for daily use of ZYN.

   The study measured the perceived relative risk of the aforementioned health conditions attributed to quitting all TNP except for the daily use of ZYN compared with quitting all TNP use.

Secondary objectives based on data from the Prospective Study were as follows:

1. Exploration of daily TNP patterns of use among ZYN users and ZYN non-users, including reasons for ZYN use, over a prospective 10-week observational period.

2. Comparison of the tendencies of ZYN users to quit TNP or use the product in an incremental fashion, in a supplemental fashion, or in complete substitution of other TNP.

4.6.2 Results and Conclusions

(b) (4)

Study findings support the conclusion that users of traditional TNP, such as smokers and smokeless tobacco users, are willing to try and continue using ZYN, specifically in substitution for their other TNP. There is no evidence of any detrimental effect to ZYN being available, and

collectively, respondents view ZYN as riskier than using no TNP, but safer than smoking or using smokeless tobacco. Specifically, the collective findings revealed the following:

- Among all TNP users, ZYN users were less likely to be smokers than ZYN non-users.
- ZYN users who were smokers had greater intention to quit smoking than ZYN non-users.
- ZYN users did not reveal intent to quit ZYN itself.
- ZYN users generally used the product as directed, with one exception of higher-than-expected tendency to keep a pouch in one's mouth for over 60 minutes.
- Respondents perceived that ZYN carries higher risk of certain adverse health conditions versus using no TNP but lower risk of those health conditions than smoking and/or using smokeless tobacco.
- Even after using ZYN for months, cigarette and moist snuff usage continue to trend downward over the observed 10-week research period.
- ZYN users who smoked also reported intention to quit smoking cigarettes that tended to increase over the 10-week period, unlike with ZYN non-users.
- The number of days per week ZYN was used slightly decreased over the 10 weeks, although the number of pouches (approximately eight pouches a day) and the duration of use remained unchanged.
- At the end of the 10 weeks, (b) (4) of ZYN users completely substituted ZYN in place of other TNP, and only (b) (4) reported smoking cigaretttes.

5 PHARMACOKINETICS, PHARMACODYNAMICS, AND ABUSE LIABILITY

It is widely accepted that nicotine is the main dependence-producing constituent in tobacco and that rate of delivery is an important determinant of abuse potential (SCENIHR 2008). In addition, the pharmacological effects of nicotine on the brain's "reward system" are also central to a smoker's liking of nicotine-delivering alternatives to cigarettes, and putatively, an important determinant of a product's efficacy for smoking cessation purposes. Orally administered nicotine cannot produce the rapid, high peaks of nicotine in arterial blood to the brain that is typically associated with smoking.

Nicotine contributes significantly to the difficulty many tobacco users experience in attempting to quit.

As with other nicotine-containing products, ZYN packaging includes the following warning:

- WARNING: This product contains nicotine. Nicotine is an addictive chemical.

Commercially available snus products in the US have a nicotine content ranging between 5 and 20 mg per pouch. Previous studies (Lunell and Curvall 2011) have indicated that on average, about 15% to 20% of the total nicotine content of snus products is extracted and absorbed, with

large inter-individual variation. When comparing the nicotine content of different nicotine-delivery products, it is important to consider that the nicotine uptake varies considerably depending on product type (tobacco versus a non-tobacco-based matrix) and product formulation (pouch geometry, water content, particle size, pH, etc.). 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. Therefore, the nicotine delivery profile of ZYN was compared with commercially available snus products (which have a documented ability to replace cigarettes as a source of recreational nicotine among current tobacco consumers).

Swedish Match has sponsored three clinical studies (Studies SM 17-01, SM 17-03, and SM 18-01) of the PK (extraction and uptake) of nicotine (Section 5.1) of different flavors and nicotine strengths of ZYN using General PSWL 1.0 g (8 mg nicotine) and American moist snuff Longhorn Pouch 18 mg as the comparator products. As noted in the FDA PMTA TPL Review 2015 for General PSWL, "these nicotine values are within the reported ranges from other marketed US moist snuff, therefore the abuse potential for these products is similar to other marketed smokeless tobacco products." The release of nicotine from a General snus PSWL (8 mg nicotine/g) following use over 30 minutes has previously been investigated (Lunell and Curvall 2011). The studies were conducted by an external contractor. The main methodological strength of these studies was their use of randomized, cross-over designs; highly standardized administration of study products; and state-of-the-art methods for the chemical and PK analyses.

Pharmacodynamic measures including changes in pulse rate (Section 5.2.1) and subjective effects for abuse liability (Section 5.2.2) were also collected in two of the clinical studies (Studies SM 17-01 and SM 17-03).

Nicotine dependence (Section 5.3) is also discussed in this section.

5.1 Pharmacokinetics of Nicotine, and Main Findings

Three clinical pharmacology studies were conducted for this PMTA to assess nicotine extraction and other PK parameters of nicotine comparing the use of ZYN to snus:

- Study SM 17-01 (Section 5.1.1)
- Study SM 17-03 (Section 5.1.2)
- Study SM 18-01 (Section 5.1.3)

These studies showed that all tested ZYN products (3, 6, and 8 mg) were associated with a nicotine exposure (AUC_{inf}) that is comparable to or lower than that from a moist snuff product representative of the market leader pouch moist snuff product. The studies did not show that nicotine extraction/delivery was affected by production technique or the use of flavors including wintergreen.

Since ZYN production in Sweden can be accomplished by (b) (4) [redacted], Studies SM 17-01 and SM 17-03 also evaluated whether there was a process effect as an additional objective.

In addition, post hoc analyses were conducted to explore the following seven hypotheses:

1. To investigate if there were any differences due to the manufacturing processes regarding both extracted amount of nicotine and PK (C_{max} and area under the plasma concentration-time curve from time zero to 120 minutes [$AUC_{[0-120]}$]) (data from Studies SM 17-01 and SM 17-03) (Section 5.1.4.1)

2. To confirm that there is no difference between ZYN Smooth 3 mg and ZYN Wintergreen 3 mg (and other flavors [Spearmint, Peppermint]) regarding the extracted amount of nicotine (data from Studies SM 17-01 and SM 17-03) (Section 5.1.4.2)

3. To confirm that there is no difference in PK (C_{max} and $AUC_{[0-120]}$) between ZYN Smooth 3 mg and ZYN Wintergreen 3 mg for the extracted amount of nicotine (data from Study SM 18-01) (Section 5.1.4.3)

4. To determine whether there is a correlation between the extracted amount of nicotine and PK (C_{max} and $AUC_{[0-120]}$) (data from Studies SM 17-03 and SM 18-01) (Section 5.1.4.4)

5. To compare the PK profiles (C_{max} and $AUC_{[0-120]}$) (data from Studies SM 17-03 and SM 18-01) (Section 5.1.4.5)

6. To investigate individual changes between different products (data from Study SM 18-01) (Section 5.1.4.6)

7. To investigate the difference in PK and extraction of nicotine between the lower and upper lip (ZYN 4.5 mg) (data from Study SM 18-01) (Section 5.1.4.7)

Furthermore, descriptive statistics were performed to assess the plasma levels of salicylate for the treatments with pouches containing Wintergreen flavor (data from Study SM 18-01) (Section 5.1.4.8).

5.1.1 Study SM 17-01

Study SM 17-01 was an open-label, randomized, 14-way cross-over, single-dose study designed to evaluate the *in vivo* extraction of nicotine and flavor compounds from ZYN compared with conventional, tobacco-based snus (General PSWL) in 20 healthy, current daily snus users.

5.1.1.1 Nicotine Extraction (Primary Endpoint)

The primary objective of Study SM 17-01 was to compare the estimated *in vivo* extracted dose of nicotine from ZYN containing 3 and 6 mg of nicotine with that from a 1.0-g General PSWL containing 8 mg of nicotine. To measure the primary endpoint, the extracted dose of nicotine from each portion was calculated by subtracting the residual amount after use from the mean of 10 unused portions. The mean (SD) extracted dose of nicotine from each pouch was calculated. The extracted dose of nicotine was analyzed using the Wilcoxon signed rank sum test and Student's t-test (paired) for within-subject difference.

5.1.1.1.1 Extracted Dose of Nicotine – Comparison Between Test and Reference Products

The Wilcoxon signed rank sum test showed statistically significant differences in extracted dose of nicotine after 15 minutes between the ZYN Smooth test products and the reference product

(General PSWL 1.0 g [8 mg]) (Table 4). The extracted dose from the test products containing 3 mg of nicotine was significantly lower compared to the reference product. The extracted dose from the test products containing 6 mg of nicotine was significantly higher compared to the reference product.

Table 4 Difference in Extracted Dose (mg) of Nicotine After 15-Minute Administration (N=18) (Study SM 17-01)

Treatment	Mean (SD)	Difference Between Products[a]	Signed Rank P-value
General PSWL 1.0 g (8 mg) - 15 min	(b) (4)		
ZYN Smooth 3 mg - 15 min			
ZYN Smooth 6 mg - 15 min			
ZYN Smooth 3 mg (AMP) - 15 min			
ZYN Smooth 6 mg (AMP) - 15 min			

Source: Section H.3.1.2.1 Report Body, Table 11.2-1, 11.2-2, 11.2-3, and 11.2-4
AMP=alternative manufacturing process; min=minutes; PSWL=portion snus white large; SD=standard deviation.
[a] General PSWL 1.0 g (8 mg) (Reference) – ZYN

There were statistically significant differences in extracted dose of nicotine after 60 minutes between the ZYN test products and the reference product (General PSWL 1.0 g [8 mg]) (Table5). The extracted dose from the test products containing 3 mg nicotine was significantly lower compared to the reference product. The extracted dose from the test products containing 6 mg was significantly higher compared to the reference product.

Table 5 Difference in Extracted Dose (mg) of Nicotine After 60-Minute Administration (N=18) (Study SM 17-01)

Treatment	Mean (SD)	Difference Between Products[a]	Signed Rank P-value
General PSWL 1.0 g (8 mg) - 60 min	(b) (4)		
ZYN Smooth 3 mg - 60 min			
ZYN Smooth 6 mg - 60 min			
ZYN Smooth 3 mg (AMP) - 60 min			
ZYN Smooth 6 mg (AMP) - 60 min			
ZYN Wintergreen 3 mg - 60 min			
ZYN Peppermint 3 mg - 60 min			
ZYN Spearmint 3 mg - 60 min			

Source: Section H.3.1.2.1 Report Body, Table 11.2-5, 11.2-6, 11.2-7, 11.2-8, 11.2-9, 11.2-10, and 11.2-11
AMP=alternative manufacturing process; min=minutes; PSWL=portion snus white large; SD=standard deviation.
[a] General PSWL 1.0 g (8 mg) (Reference) – ZYN

A linearity between 15 and 60 minutes seemed to be established for the reference and test products (Section H.3.1.2.1 Report Body, Figure 14.3-1). However, the individual variation between subjects was high for the 60-minute assessment.

Summary statistics of extracted dose of nicotine are presented in Section H.3.1.2.1 Report Body, Table 14.3-1. The distribution of extracted dose of nicotine is presented by product in

Section H.3.1.2.1 Report Body, Figure 14.3-1. Individual subject data are provided in Section H.3.1.2.1 Appendix 16.2.6.

5.1.1.1.2 Extracted Dose of Nicotine – Pairwise Comparison Between Test Products

Between the two manufacturing process techniques, there were no statistically significant differences in extracted dose of nicotine between ZYN Smooth 3 mg and 6 mg compared to ZYN Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 minutes or 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-2 to Table 14.3-5).

Among the flavors tested, there were no statistically significant differences between ZYN Smooth 3 mg compared to ZYN Wintergreen 3 mg, ZYN Peppermint 3 mg, or ZYN Spearmint 3 mg administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-6 to Table 14.3-8).

5.1.1.1.3 Extracted Dose of Nicotine (Rate of Extraction) – Comparison Between Test and Reference Products

The Wilcoxon signed rank sum test showed statistically significant differences in rate of extraction between the test products and the reference product (General PSWL 1.0 g [8 mg]) administered during 15 and 60 minutes (Section H.3.1.2.1 Report Body, Table 11.2-23 to Table 11.2-33). The rate of extraction for the test products was significantly higher compared to the reference product.

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

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

5.1.1.1.4 Extracted Dose of Nicotine (Rate of Extraction) – Pairwise Comparison Between the Test Products

There were no statistically significant differences in rate of extraction between ZYN Smooth 3 mg and 6 mg compared to ZYN Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 or 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-16 to Table 14.3-19). There were no statistically significant differences between ZYN Smooth 3 mg compared to ZYN Wintergreen 3 mg, ZYN Peppermint 3 mg, or ZYN Spearmint 3 mg administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-20 to Table 14.3-22).

5.1.2 Study SM 17-03

Study SM 17-03 was an open-label, randomized, five-way cross-over, single-dose study to assess nicotine PK and subjective effects of a single dose of a ZYN compared with conventional, tobacco-based snus (General PSWL) among current healthy daily snus users. PK blood sampling

was performed before (0) and at 5, 10, 15, 30, and 60 minutes and 1.5, 2, 4, and 6 hours after each application of the IPs.

The primary endpoint was AUC_{inf} based on plasma concentrations of nicotine after administration of a single dose of ZYN containing 3 and 6 mg of nicotine to that of a single dose from a 1-g General PSWL containing 8 mg of nicotine. Secondary PK endpoints were as follows:

- AUC_{60min}, C_{max}, t_{max}, $AUC_{0\text{-}last}$, and $t_{½}$ (z) of ZYN compared to General PSWL
- *In vivo* extracted amount of nicotine
- Correlation between the estimates of AUC_{inf} and the total amount of nicotine extracted from ZYN

5.1.2.1 AUC_{inf} (Primary Endpoint)

5.1.2.1.1 AUC_{inf} – Comparison Between Test and Reference Products

There were statistically significant differences in mean AUC_{inf} between each of the four test products and the reference product (General PSWL 1.0 g [8 mg]) (Table 6). The mean AUC_{inf} of both ZYN Smooth 3 mg products was significantly lower compared to that of the reference product. The AUC_{inf} for both ZYN Smooth 6 mg products was significantly higher compared to the reference product.

Summary statistics of AUC_{inf} are presented in Section H.3.1.2.2 Report Body, Table 11.3-10.

Table 6 Difference in AUC_{inf} (min*ng/mL) Between Test and Reference Products (N=17) (Study SM 17-03)

Treatment	Mean (SD)	Difference Between Products[a]	Signed Rank P-value
General PSWL 1.0 g (8 mg)	[redacted]		
ZYN Smooth 3 mg			
ZYN Smooth 3 mg (AMP)			
ZYN Smooth 6 mg			
ZYN Smooth 6 mg (AMP)			

Source: Section H.3.1.2.2 Report Body, Tables 11.2-1, 11.2-2, 11.2-3, and 11.2-4
AMP=alternative manufacturing process; AUC_{inf}=area under the plasma concentration-time curve from time zero to infinity; min=minutes; PSWL=portion snus white large; SD=standard deviation.
[a] Difference between General PSWL 1.0 g (8 mg) (Reference) and ZYN

5.1.2.1.2 AUC_{inf} – Pairwise Comparison Between the Test Products

Statistically significant differences in AUC_{inf} were observed between the following test products:

- 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 in AUC_{inf} observed between the following test products:

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

See Section H.3.1.2.2 Report Body, Table 14.3-1 to Table 14.3-6 for detailed information.

5.1.2.2 Nicotine Extraction (Secondary Endpoint)

5.1.2.2.1 Nicotine Extraction – Comparison Between Test and Reference Products

Statistically significant differences were observed in the extracted amount of nicotine between each of the four test products and the reference product (General PSWL 1.0 g [8 mg]) (Table 7). 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 both ZYN Smooth 6 mg products was significantly higher compared to the reference product.

Table 7 Difference in Extracted Nicotine (mg) Between Test and Reference Products (N=17) (Study SM 17-03)

Treatment	Mean (SD)	Difference Between Products[a]	Signed Rank P-value
General PSWL 1.0 g (8 mg)	(b) (4)		
ZYN Smooth 3 mg			
ZYN Smooth 3 mg (AMP)			
ZYN Smooth 6 mg			
ZYN Smooth 6 mg (AMP)			

Source: Section H.3.1.2.2 Report Body, Tables 11.3-2, 11.3-3, 11.3-4, and 11.3-5
AMP=alternative manufacturing process; min=minutes; PSWL=portion snus white large; SD=standard deviation.
[a] Difference between General PSWL 1.0 g (8 mg) (Reference) and ZYN

5.1.2.2.2 Nicotine Extraction – Pairwise Comparison Between the Test Products

Statistically significant differences in the extracted amount of nicotine were observed between the following test products:

- 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) (However, the results were not clinically relevant.)

There were no statistically significant difference in the extracted amount of nicotine observed between the ZYN Smooth 3 mg and 3 mg (alternative manufacturing process) test products.

See Section H.3.1.2.2 Report Body, Table 14.3-27 to Table 14.3-32 for detailed information.

5.1.2.2.3 Rate of Nicotine Extraction – Comparison Between Test and Reference Products

The rate of extraction for each of test products was statistically significantly higher compared to the reference product (General PSWL 1.0 g [8 mg]) (Table 8).

Table 8 Difference in Rate of Extraction (%) Between Test and Reference Products (N=17) (Study SM 17-03)

Treatment	Mean (SD)	Difference Between Products[a]	Signed Rank P-value
General PSWL 1.0 g (8 mg)	(b) (4)		
ZYN Smooth 3 mg			
ZYN Smooth 3 mg (AMP)			
ZYN Smooth 6 mg			
ZYN Smooth 6 mg (AMP)			

Source: Section H.3.1.2.2 Report Body, Tables 11.3-6, 11.3-7, 11.3-8, and 11.3-9
AMP=alternative manufacturing process; min=minutes; PSWL=portion snus white large; SD=standard deviation.
[a] Difference between General PSWL 1.0 g (8 mg) (reference) and ZYN

5.1.2.2.4 Rate of Nicotine Extraction – Pairwise Comparison Between the Test Products

A statistically significant difference in the rate of extraction was observed between the ZYN Smooth 3 mg and 3 mg (alternative manufacturing process) test products; however, the results were not clinically relevant. There were no statistically significant differences in the extracted amount of nicotine observed between the following test products:

- 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)

See Section H.3.1.2.2 Report Body, Table 14.3-33 to Table 14.3-38 for detailed information.

5.1.2.3 Correlations – AUC_{inf} and Extracted Nicotine (Secondary Endpoint)

Scatter plots of mean AUC_{inf} against extracted nicotine are presented for each treatment, respectively, together with a fitted linear regression line in Section H.3.1.2.2 Report Body, Figure 14.3-1 to Figure 14.3-5. 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 Section H.3.1.2.2 Report Body, Figure 14.3-6 to Figure 14.3-10. For all treatment groups, the regression lines seem to demonstrate a correlation. However, the correlations are judged to be relatively low based on the r^2 values ranging from 0.14 to 0.45.

5.1.2.4 Nicotine Plasma Concentration (Secondary Endpoint)

5.1.2.4.1 Nicotine Plasma Concentration – Comparison Between Test and Reference Products

Nicotine concentrations before (0) and 5, 10, 15, 30, and 60 minutes and 1.5, 2, 4, and 6 hours after administration are presented in Figure 1 and summarized by treatment in Section H.3.1.2.2 Report Body, Table 14.3-49.

Figure 1 Mean Plasma Concentrations of Nicotine (ng/mL) (Study SM 17-03)

Source: Section H.3.1.2.2 Report Body, Figure 11.3-1
PSWL=portion snus white large; Swedish portion snus PSWL=General PSWL.

There were statistically significant differences between each of the four test products and the reference product (General PSWL 1.0 g [8 mg]), respectively, for a majority of time points from 10 to 15 minutes until 6 hours after administration (Section H.3.1.2.2 Report Body, Table 14.3-39 to Table 14.3-42). The nicotine plasma concentrations from both the ZYN Smooth 3 mg products were significantly lower compared to those of the reference product. The plasma concentrations from both the ZYN Smooth 6 mg products were significantly higher compared to the reference product.

5.1.2.4.2 Nicotine Plasma Concentration – Pairwise Comparison Between the Test Products

Statistically significant differences in nicotine plasma concentrations were observed at the majority of time points from 5 to 10 minutes until 6 hours after administration between the following test products:

- 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 in nicotine plasma concentrations observed at any time point between the following test products:

- ZYN Smooth 3 mg and 3 mg (alternative manufacturing process)
- ZYN Smooth 6 mg and 6 mg (alternative manufacturing process) - except at 60 minutes after administration

See Section H.3.1.2.2 Report Body, Table 14.3-43 to Table 14.3-48 for detailed information.

5.1.2.5 Pharmacokinetic Parameters (Secondary Endpoints)

A summary of the PK parameters by treatment is provided in Table 9. Individual subject data are provided in Section H.3.1.2.2 Appendix 16.2.6.

Table 9 Pharmacokinetic Parameters by Treatment (N=17) (Study SM 17-03)

Treatment	Analyte (unit)	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN Smooth 3 mg	AUC_{inf} (min*ng/mL)	(b) (4)					
	AUC_{60min} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	$t_{½}$ (z) (min)						
	C_{max} (ng/mL)						
	t_{max} (min)						
ZYN Smooth 6 mg	AUC_{inf} (min*ng/mL)						
	AUC_{60min} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	$t_{½}$ (z) (min)						
	C_{max} (ng/mL)						
	t_{max} (min)						
ZYN Smooth 3 mg (AMP)	AUC_{inf} (min*ng/mL)						
	AUC_{60min} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	$t_{½}$ (z) (min)						
	C_{max} (ng/mL)						
	t_{max} (min)						
ZYN Smooth 6 mg (AMP)	AUC_{inf} (min*ng/mL)						
	AUC_{60min} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	$t_{½}$ (z) (min)						
	C_{max} (ng/mL)						
	t_{max} (min)						

Treatment	Analyte (unit)	Min	Median	Max	Mean	CV (%)	Geometric Mean
General PSWL 1.0 g (8 mg)	AUC_{inf} (min*ng/mL)	(b) (4)					
	AUC_{60min} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	$t_{½}$ (z) (min)						
	C_{max} (ng/mL)						
	t_{max} (min)						

Source: Section H.3.1.2.2 Report Bo

AMP=alternative manufacturing process; AUC_{inf}=area under the plasma concentration-time curve from time zero to infinity; AUC_{60min}=area under the plasma concentration-time curve from time zero to 60 minutes; $AUC_{0\text{-}last}$=area under the plasma concentration-time curve from time zero to last observation; C_{max}=maximum concentration; CV=coefficient of variation; Max=maximum; min=minutes; Min=minimum; PSWL=portion snus white large; $t_{½}$ (z)=terminal half-life; t_{max}=time to maximum concentration.

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

5.1.2.5.1 Pharmacokinetic Parameters – Comparison Between Test and Reference Products

Statistically significant differences between each of the four test products and the reference product (General PSWL 1.0 g [8 mg]) were shown for $AUC_{0\text{-}last}$, AUC_{60min}, and C_{max} (Section H.3.1.2.2 Report Body, 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, respectively).

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

There were no statistically significant differences between any of the four test products and the reference product in terms of $t_{½}$ (z) or t_{max} (Section H.3.1.2.2 Report Body, Table 14.3-80 to Table 14.3-83 and Table 14.3-90 to Table 14.3-93, respectively).

5.1.2.5.2 Pharmacokinetic Parameters – Pairwise Comparison Between the Test Products

For $AUC_{0\text{-}last}$, AUC_{60min}, and C_{max}, there were statistically significant differences between the following test products:

- 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 the following test products:

- ZYN Smooth 3 mg (alternative manufacturing process) and 6 mg (alternative manufacturing process)
- ZYN Smooth 6 mg and 6 mg (alternative manufacturing process) (However, the results were not clinically relevant.)

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

Details are provided in Section H.3.1.2.2 Report Body, 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.

5.1.3 Study SM 18-01

Study SM 18-01 was an open-label, randomized, seven-way cross-over, single-dose study to assess nicotine plasma concentrations and PK of a single dose (60 minutes) of ZYN compared with conventional, tobacco-based snus (General PSWL) and American moist snuff (Longhorn moist snuff pouch) among current healthy daily snus users. PK blood sampling was performed before (0) and at 5, 10, 15, 30 60, 90, 120, 240, and 360 minutes after each application of the IPs.

The primary endpoint was AUC_{inf} based on plasma concentrations of nicotine after administration of a single dose of ZYN Smooth containing 6 mg of nicotine compared to that of one single dose of two pouches of General PSWL 8 mg. However, upon analysis of data, it was revealed that ZYN Smooth 6 mg and ZYN Wintergreen 6 mg contained a smaller amount of nicotine than intended (approximately 4.5 mg rather than 6 mg) and were hence excluded from all comparisons and analyses. The intended comparisons of AUC_{inf} were only performed between the other IPs (ie, between the ZYN Smooth 8 mg product and General PSWL 2 × 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg).

Secondary endpoints were as follows:

- t_{max}, C_{max}, AUC_{inf}, $AUC_{0\text{-}last}$, and $t_{½}$ (z) of ZYN Smooth, General PSWL, and Longhorn moist snuff pouches
- Nicotine plasma concentrations for the ZYN Wintergreen and Longhorn Wintergreen treatments compared to the corresponding non-wintergreen flavored products, respectively
- Nicotine plasma concentrations for the upper lip and lower lip placement of ZYN Smooth
- *In-vivo* extracted amount of nicotine from all products
- Pairwise analysis of *in-vivo* extracted nicotine and rate of extraction
- Plasma levels of salicylate for products containing Wintergreen flavor

5.1.3.1 AUC_{inf} (Primary Endpoint)

5.1.3.1.1 AUC_{inf} – Comparison Between Test and Reference Products

The highest mean AUC_{inf} was observed following a single dose of General PSWL 2 × 8 mg and the lowest following a single dose of ZYN Smooth 8 mg (Table 10). The difference was statistically significant (p=0.0001; Section H.3.1.2.3 Report Body, Table 14.3-1). The mean AUC_{inf} following a single dose of General PSWL 2 × 8 mg was also significantly higher than the mean AUC_{inf} of both Longhorn Natural 18 mg (p=0.0023; Section H.3.1.2.3 Report Body, Table 14.3-4) and Longhorn Wintergreen 18 mg (p=0.0091; Section H.3.1.2.3 Report Body, Table 14.3-5).

There were no statistically significant differences in mean AUC_{inf} between ZYN Smooth 8 mg and either Longhorn Natural 18 mg or Longhorn Wintergreen 18 mg (Section H.3.1.2.3 Report Body, Table 14.3-2 and Table 14.3-3) or between Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg (Section H.3.1.2.3 Report Body, Table 14.3-6).

Corresponding results for the baseline adjusted comparisons are provided in Section H.3.1.2.3 Report Body, Table 14.3-7 to Table 14.3-12. Individual data are listed in Section H.3.1.2.3 Appendix 16.2.6.

Table 10 AUC_{inf} (min*ng/mL) by Treatment (N=29; PPS) (Study SM 18-01)

Treatment	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN Smooth [redacted] mg	(b) (4)					
General PSWL 2 × 8 mg						
Longhorn Natural 18 mg						
Longhorn Wintergreen 18 mg						

Source: Section H.3.1.2.3 Report Body, Table 11.2-1
AUC_{inf}=area under the plasma concentration-time curve from time zero to infinity; CV=coefficient of variation; Max=maximum; Min=minimum; PPS=per-protocol analysis set; PSWL=portion snus white large.
Min and max values have been rounded to three significant digits. CV, mean, median, and geometric mean have been rounded to four significant digits.

5.1.3.2 Nicotine Extraction (Secondary Endpoint)

5.1.3.2.1 Nicotine Extraction – Comparison Between Test and Reference Products

The mean extracted dose of nicotine from General PSWL 2 × 8 mg pouches (b) (4) mg) was significantly higher than the mean extracted dose from ZYN Smooth 8 mg (b) (4) , Longhorn Natural 18 mg (b) (4) and Longhorn Wintergreen 18 mg (b) (4) (Table 11; Section H.3.1.2.3 Report Body, Table 11.3-1, Table 14.3-13, Table 14.3-16, and Table 14.3-17).

In addition, the mean extracted dose of nicotine from ZYN Smooth 8 mg (b) (4) mg) was significantly higher than the mean amount extracted from Longhorn Natural 18 mg (b) (4) (b) (4) , whereas there were no statistically significant differences in the extracted dose of nicotine between ZYN Smooth 8 mg and Longhorn Wintergreen 18 mg or between Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg (Table 11; Section H.3.1.2.3 Report Body, Table 11.3-1, Table 14.3-14, Table 14.3-15, and Table 14.3-18).

The nicotine contents in the unused pouches used for the calculations are listed and summarized in Section H.3.1.2.3 Report Body, Table 14.3-19. Individual extraction data are provided in Section H.3.1.2.3 Appendix 16.2.6.

Table 11 Extracted Nicotine Results (mg) (N=30; PPS) (Study SM 18-01)

Treatment	Min	Max	Mean	Median	SD
ZYN Smooth 8 mg	(b) (4)				
General PSWL 2 × 8 mg					
Longhorn Natural 18 mg					
Longhorn Wintergreen 18 mg					

Source: Section H.3.1.2.3 Report Body, Table 11.3-1
Max=maximum; Min=minimum; PPS=per-protocol analysis set; PSWL=portion snus white large; SD=standard deviation.

5.1.3.2.2 Correlations – AUC_{inf} and Extracted Nicotine

Scatter plots of mean AUC_{inf} against extracted nicotine are presented for ZYN Smooth 8 mg, General PSWL 2 × 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg in Section H.3.1.2.3 Report Body, Figure 14.3-1 to Figure 14.3-4 (non-baseline-adjusted data) and Figure 14.3-5 to Figure 14.3-8 (baseline-adjusted data). The regression lines demonstrated a correlation (ie, above 0.5) for all IPs except General PSWL 2 × 8 mg; both non-baseline adjusted and baseline adjusted data showed a strong relationship between AUC_{inf} and extracted amount of nicotine, ie, high AUC_{inf} values correspond to high amounts of extracted nicotine.

5.1.3.2.3 Rate of Nicotine Extraction – Comparison Between Test and Reference Products

The mean rate of nicotine extraction from ZYN Smooth 8 mg (b) (4) was significantly higher than that from General PSWL 2 × 8 mg (b) (4) Longhorn Natural 18 mg (b) (4), and Longhorn Wintergreen 18 mg (b) (4) (Section H.3.1.2.3 Report Body, Table 14.3-20, Table 14.3-21, and Table 14.3-22).

In addition, the rate of nicotine extraction from General PSWL 2 × 8 mg (b) (4) was significantly higher than the rate of extraction from Longhorn Natural 18 mg (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-23) and Longhorn Wintergreen 18 mg (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-24).

There were no statistically significant differences in the rate of nicotine extraction between Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg (Section H.3.1.2.3 Report Body, Table 14.3-25).

Individual rates of extraction data are provided in Section H.3.1.2.3 Appendix 16.2.6.

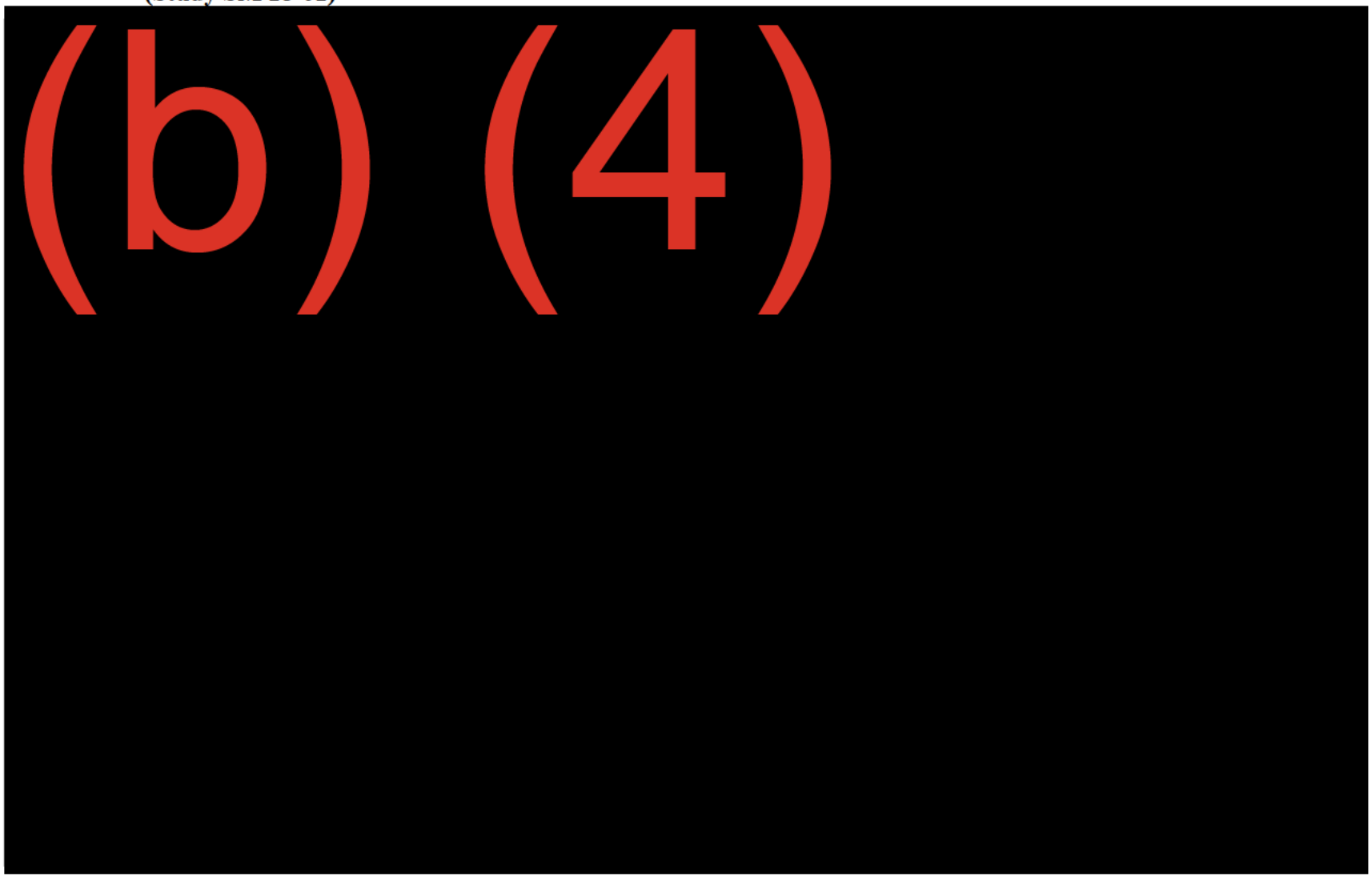
5.1.3.3 Nicotine Plasma Concentrations (Secondary Endpoint)

Nicotine plasma concentrations are summarized by treatment for ZYN Smooth 8 mg, General PSWL 2 × 8 mg, Longhorn Natural 18 mg, and Longhorn Wintergreen 18 mg in Section H.3.1.2.3 Report Body, Table 14.3-26 and are displayed in Figure 2 (before and 5, 10, 15, 30, 60, 90, 120, 240, and 360 minutes after administration of IP). The plasma concentration

versus time curves were similar for all IPs, with the highest concentrations of nicotine observed at one hour after the start of IP administration in association with the removal of the IP.

Individual data are displayed by treatment in Section H.3.1.2.3 Report Body, Figure 14.3-9 to Figure 14.3-12. Individual data for all treatments are listed in Section H.3.1.2.3 Appendix 16.2.5.

Figure 2 Mean Concentrations of Nicotine (ng/mL) vs Time for Investigational Products (Per-protocol Analysis Set) (Study SM 18-01)



Source: Section H.3.1.2.3 Report Body, Figure 11.3-1
BLQ=below limit of quantification; LLOQ=lower limit of quantification; PSWL=portion snus white large.

5.1.3.4 Pharmacokinetic Parameters (Secondary Endpoints)

A summary of the PK parameters by IP is provided in Table 12 (non-baseline-adjusted data) and in Section H.3.1.2.3 Report Body, Table 14.3-28 (baseline-adjusted data). Individual subject data are provided in Section H.3.1.2.3 Appendix 16.2.6.

Table 12 Pharmacokinetic Parameters by Investigational Product (N=29; PPS) (Study SM 18-01)

Treatment	Analyte (unit)	Min	Median	Max	Mean	CV (%)	Geometric Mean
ZYN Smooth 8 mg	AUC_{inf} (min*ng/mL)	(b) (4)					
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	C_{max} (ng/mL)						
	$t_{½}$ (z) (min)						
	t_{max} (min)						
General PSWL 2 × 8 mg	AUC_{inf} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	C_{max} (ng/mL)						
	$t_{½}$ (z) (min)						
	t_{max} (min)						
Longhorn Natural 18 mg	AUC_{inf} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	C_{max} (ng/mL)						
	$t_{½}$ (z) (min)						
	t_{max} (min)						
Longhorn Wintergreen 18 mg	AUC_{inf} (min*ng/mL)						
	$AUC_{0\text{-}last}$ (min*ng/mL)						
	C_{max} (ng/mL)						
	$t_{½}$ (z) (min)						
	t_{max} (min)						

Source: Section H.3.1.2.3 Report Body, Table 11.3-2

AUC_{inf}=area under the plasma concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$=area under the plasma concentration-time curve from time zero to last observation; C_{max}=maximum concentration; CV=coefficient of variation; Max=maximum; min=minutes; Min=minimum; PPS=perprotocol analysis set; PSWL=portion snus white large; $t_{½}$ (z)=terminal half-life; t_{max}=time to maximum concentration.

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

5.1.3.4.1 Pharmacokinetic Parameters – Comparison Between Test and Reference Products

$AUC_{0\text{-last}}$

As for AUC_{inf}, the highest mean $AUC_{0\text{-last}}$ was observed following a single dose of General PSWL 2 × 8 mg and the lowest following a single dose of ZYN Smooth 8 mg (Section H.3.1.2.3 Report Body, Table 11.3-2). The difference was statistically significant (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-29). The mean AUC_{inf} following a single dose of General PSWL 2 × 8 mg was also significantly higher than the mean AUC_{inf} of both Longhorn Natural 18 mg (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-32) and Longhorn Wintergreen 18 mg (b) (4) ; Section H.3.1.2.3 Report Body, Table 14.3-33).

There were no statistically significant differences in mean $AUC_{0\text{-last}}$ between ZYN Smooth 8 mg and either Longhorn Natural 18 mg or Longhorn Wintergreen 18 mg or between Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg (Section H.3.1.2.3 Report Body, Table 14.3-30, Table 14.3-31, and Table 14.3-34).

Corresponding results for baseline-adjusted data are provided in Section H.3.1.2.3 Report Body, Table 14.3-53 to Table 14.3-58.

C_{max}

The highest mean C_{max} was observed following a single dose of General PSWL 2 × 8 mg (b) (4) and the lowest following a single dose of Longhorn Natural 18 mg (b) (4) Section H.3.1.2.3 Report Body, Table 11.3-2). The difference was statistically significant (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-38). The mean C_{max} of General PSWL 2 × 8 mg was also significantly higher than those of ZYN Smooth 8 mg (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-35) and Longhorn Wintergreen 18 mg (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-39).

There were no statistically significant differences in mean C_{max} between ZYN Smooth 8 mg and either Longhorn Natural 18 mg or Longhorn Wintergreen 18 mg, respectively, or between Longhorn Natural 18 mg and Longhorn Wintergreen 18 mg (Section H.3.1.2.3 Report Body, Table 14.3-36, Table 14.3-37, and Table 14.3-40).

Corresponding results were found for baseline-adjusted data (Section H.3.1.2.3 Report Body, Table 14.3-59 to Table 14.3-64).

t_{max}

Mean t_{max} was around one hour for all products (range: 57 minutes [ZYN Smooth 8 mg] to 64 minutes [Longhorn Wintergreen 18 mg]). The mean t_{max} of ZYN Smooth 8 mg was significantly shorter than the mean t_{max} of Longhorn Wintergreen 18 mg (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-43). Otherwise, there were no statistically significant differences between the products in terms of t_{max} (Section H.3.1.2.3 Report Body, Table 14.3-41 to Table 14.3-42 and Table 14.3-44 to Table 14.3-46).

Corresponding results were found for baseline-adjusted data except that the mean t_{max} of ZYN Smooth 8 mg was also significantly shorter than the mean t_{max} of General PSWL 2 × 8 mg (Section H.3.1.2.3 Report Body, Table 14.3-65 to Table 14.3-70).

$t_{1/2}$ (z)

The mean $t_{½}$ (z) of ZYN Smooth 8 mg was significantly shorter than the mean $t_{½}$ (z) of Longhorn Wintergreen 18 mg (b) (4) Section H.3.1.2.3 Report Body, Table 14.3-49). Otherwise, there were no statistically significant differences between the products in terms of $t_{½}$ (z) (Section H.3.1.2.3 Report Body, Table 14.3-47, Table 14.3-48, and Table 14.3-50 to Table 14.3-52).

Corresponding results were found for baseline-adjusted data (Section H.3.1.2.3 Report Body, Table 14.3-71 to Table 14.3-76).

5.1.3.5 Analysis of Plasma Levels of Salicylate for Products Containing Wintergreen

The plasma levels of salicylate for Longhorn Wintergreen 18 mg are summarized in Section H.3.1.2.3 Report Body, Table 14.3-27. Quite strikingly, approximately half of the subjects for whom salicylate was analyzed had measurable concentrations of salicylate prior to intake of both Longhorn Wintergreen 18 mg and ZYN Wintergreen 6 mg (4.5 mg) (Section H.3.1.2.3 Appendix 16.2.5). However, none of the subjects reported that they had taken any concomitant medications (b) (4) (Swain et al 1985).

5.1.4 Post Hoc Pharmacokinetic Analyses

For the post hoc PK analyses of Studies SM 17-01, SM 17-03, and SM 18-01, the statistical and analytical plan is provided in Section H.3.1.2.4 Report, Section 3. For each analysis, only the PPS was used from each study. Pharmacokinetic parameters was calculated by non-compartmental analysis according to the linear up-log down method using Phoenix WinNonlin version 8.1. No adjustment for multiple comparison/multiplicity was performed, and a significance level of 5% was applied.

5.1.4.1 Hypothesis 1: Differences in the Manufacturing Processes for Extracted Amount of Nicotine

Since ZYN production can be accomplished by either manual process or fluid bed process, Studies SM 17-01 and SM 17-03 also evaluated whether there was a process effect as an additional objective. In order to investigate if there were any differences in the manufacturing processes regarding both the extracted amount of nicotine and PK (C_{max} and $AUC_{[0-120]}$), the following comparisons were made from Studies SM 17-01 and SM 17-03:

- ZYN Smooth 3 mg from Study SM 17-01 versus Study SM 17-03
- ZYN Smooth 3 mg (alternative manufacturing process) from Study SM 17-01 versus Study SM 17-03

- ZYN Smooth 6 mg from Study SM 17-01 versus Study SM 17-03

ZYN Smooth 6 mg (alternative manufacturing process) from Study SM 17-01 versus Study SM 17-03Since there were no differences observed in the comparisons above, the following comparisons were also made:

- ZYN Smooth 3 mg (Studies SM 17-01 and SM 17-03) versus ZYN Smooth 3 mg (alternative manufacturing process) (Studies SM 17-01 and SM 17-03)

- ZYN Smooth 6 mg (Studies SM 17-01 and SM 17-03) versus ZYN Smooth 6 mg (alternative manufacturing process) (Studies SM 17-01 and SM 17-03)

There were no statistically significant differences in any of the comparisons (Section H.3.1.2.4 Report, Table 14.1.1 to Table 14.1.10). Therefore, data for ZYN Smooth 3 mg for both manufacturing processes were pooled together, and the same pooling was done with data for ZYN Smooth 6 mg (both manufacturing processes).

5.1.4.2 Hypothesis 2: Difference in Flavors for Extracted Amount of Nicotine

In order to test that there is no difference between ZYN Smooth 3 mg and ZYN 3 mg Wintergreen and other flavors (Spearmint, Peppermint) regarding the extracted amount of nicotine, the ZYN 3 mg pooled data (both manufacturing processes from Studies SM 17-01 and SM 17-03) were used in the analyses of the following comparisons:

- ZYN Smooth 3 mg versus all other ZYN 3 mg flavors (Wintergreen, Peppermint, and Spearmint)

- Each ZYN 3 mg flavor pairwise

- ZYN Smooth 3 mg versus the mean of the three other ZYN 3 mg flavors (Wintergreen, Peppermint, and Spearmint)

There were no statistically significant differences in any of the comparisons (Section H.3.1.2.4 Report, Table 14.2.1 to Table 14.2.7). Therefore, data from all flavored ZYN 3 mg were pooled together with the pooled ZYN 3 mg data from Hypothesis 1 for further analyses.

5.1.4.3 Hypothesis 3: Difference in PK Between Wintergreen Flavor for Extracted Amount of Nicotine

Since the flavoring agent (b) (4) has been hypothesized to facilitate oral nicotine uptake, nicotine extraction and PK analyses were performed in Study SM 18-01.

In order to test that there is no difference in PK (C_{max} and $AUC_{[0-120]}$) between Wintergreen flavor and no flavor for the extracted amount of nicotine, the following comparisons were performed on data from Study SM 18-01:

- ZYN Wintergreen 4.5 mg versus ZYN Smooth 4.5 mg

- Longhorn Wintergreen versus Longhorn Natural

There were no statistically significant differences found between Longhorn Natural and Longhorn Wintergreen (Section H.3.1.2.4 Report, Table 14.3.1 to Table 14.3.3).

As shown in Table 13, there was no statistically significant difference in the extracted amount of nicotine found between ZYN Smooth and ZYN Wintergreen; however, both $AUC_{(0-120)}$ and C_{max} were statistically significantly larger in ZYN Smooth compared to ZYN Wintergreen.

Table 13 ZYN Smooth 4.5 mg versus ZYN Wintergreen 4.5 mg for Extracted Amount of Nicotine, $AUC_{(0-120)}$, and C_{max}

	ZYN Smooth 4.5 mg (n=30)	ZYN Wintergreen 4.5 mg (n=30)	T-test P-value
Extracted amount of nicotine			
Mean (SD)			
Median (Min, Max)			
Q1, Q3 (IQR)			
$AUC_{(0-120)}$			
Mean (SD)			
Median (Min, Max)			
Q1, Q3 (IQR)			
C_{max}			
Mean (SD)			
Median (Min, Max)			
Q1, Q3 (IQR)			

Source: Section H.3.1.2.4 Report, Table 14.3.4, Table 14.3.5, and Table 14.3.6
$AUC_{(0-120)}$=area under the plasma concentration-time curve from time zero to 120 minutes; C_{max}=maximum concentration; IQR=interquartile range; Max=maximum; Min=minimum; Q=quartile; SD=standard deviation.
P-values have been rounded to three decimal places.

5.1.4.4 Hypothesis 4: Correlation Between the Extracted Amount of Nicotine and PK Parameters

Correlations between the extracted amount of nicotine, C_{max}, and $AUC_{(0-120)}$ were calculated for the following groups:

- ZYN Smooth 3 mg (both manufacturing processes) from Study 17-03 (Section H.3.1.2.4 Report, Table 14.4.1)
- ZYN Smooth 4.5 mg from Study 18-01 (Section H.3.1.2.4 Report, Table 14.4.2)
- ZYN Wintergreen 4.5 mg from Study 18-01 (Section H.3.1.2.4 Report, Table 14.4.3)
- ZYN Smooth 6 mg (both manufacturing processes) from Study 17-03 (Section H.3.1.2.4 Report, Table 14.4.4)
- ZYN Smooth 8 mg from Study 18-01 (Section H.3.1.2.4 Report, Table 14.4.5)

- General PSWL 8 mg from Study 17-03 (Section H.3.1.2.4 Report, Table 14.4.6)
- General PSWL (2 × 8mg) from Study 18-01 (Section H.3.1.2.4 Report, Table 14.4.7)

All of the correlations were high (>0.62) and statistically significant (all p<0.0001).

5.1.4.5 Hypothesis 5: Compare the PK Profile

The PK profile ($AUC_{[0\text{-}120]}$ and C_{max}) plotted across groups from Studies SM 17-03 and SM 18-01 is presented in Figure 3 and Figure 4, respectively. The slopes for both $AUC_{(0\text{-}120)}$ and C_{max} were significant (p<0.0001 for both) and positive (ie, increasing milligrams in the ZYN products correspond to increases in both $AUC_{[0\text{-}120]}$ and C_{max}) (adjusted R2: 0.3803 for $AUC_{(0\text{-}120)}$ and 0.3285 for C_{max}; Section H.3.1.2.4 Report, Table 14.5.1 and Table 14.5.2, respectively). There seemed to be a linear relation between the ZYN product nicotine strength and the PK variables. This data demonstrates that ZYN 3 mg and 6 mg deliver nicotine in the range of already established smokeless products on the market.

Figure 3 Boxplot of $AUC_{(0\text{-}120)}$ by Treatment Group (Studies SM 17-03 and SM 18-01)

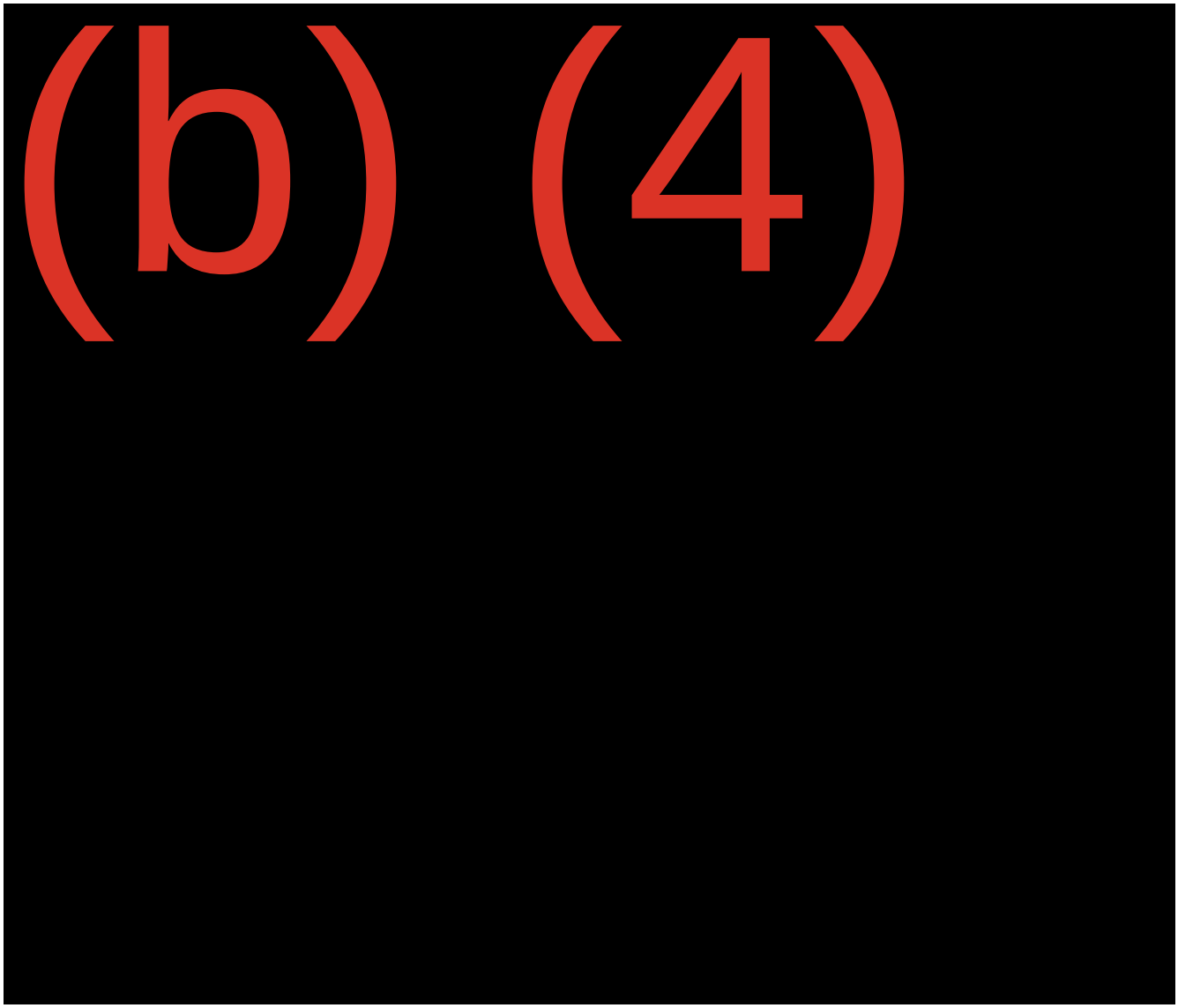
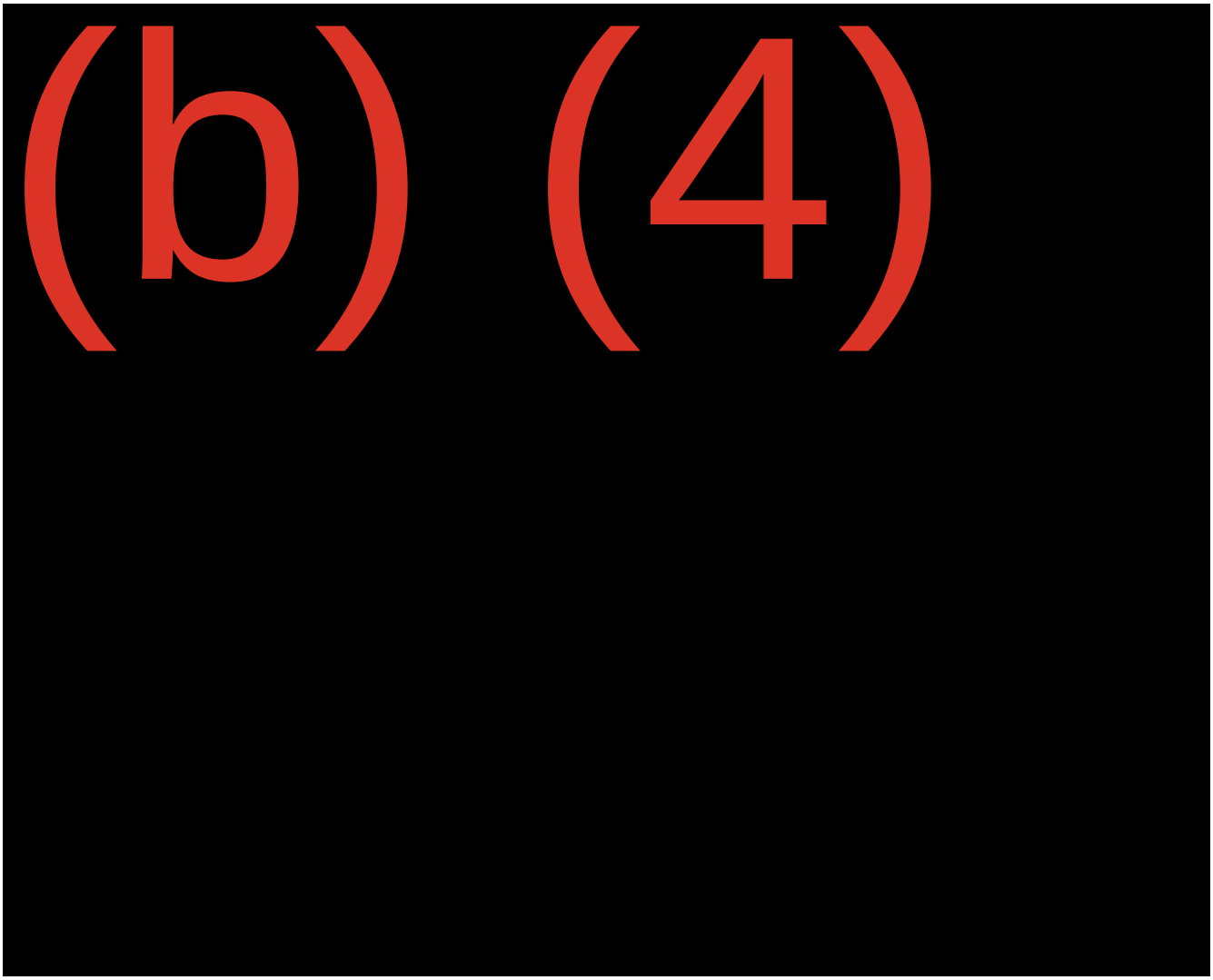


Figure 4 Boxplot of C_{max} by Treatment Group (Studies SM 17-03 and SM 18-01)



5.1.4.6 Hypothesis 6: Individual Changes Between Different Products

The majority of observations were within ±1 SD (Section H.3.1.2.4 Report, Section 5.6 and Table 14.6.1 through Table 14.6.15). The correlations between the Study SM 18-01 products for the extracted amount of nicotine, C_{max}, and $AUC_{(0-120)}$ were higher for the ZYN products (Smooth 4.5 mg, Smooth 8 mg, and Wintergreen 4.5 mg) compared to the other reference products (General PSWL [2 × 8 mg] and Longhorn [Natural and Wintergreen]) (Section H.3.1.2.4 Report, Table 14.6.11).

5.1.4.7 Hypothesis 7: Difference in PK and Extraction of Nicotine Between the Lower and Upper Lip

Comparisons were made in extracted amount of nicotine, C_{max}, and $AUC_{(0-120)}$ between the lower lip and upper lip (ie, the intended use) administration of ZYN Smooth 4.5 mg in Study SM 18-01. The extracted amounts of nicotine, C_{max}, and $AUC_{(0-120)}$ were all statistically significantly higher for the lower lip administration (Section H.3.1.2.4 Report, Table 14.7.1, Table 14.7.2, and Table 14.7.3, respectively).

5.1.4.8 Plasma Levels of Salicylate (Wintergreen Flavor)

In Study SM 17-01, the extracted amount of (b) (4) during use was calculated by using the average reference concentration of (b) (4) by weight (in mg/g in 10 unused pouches) and multiplying this value with the individual, measured weight of each pouch used in the study. From this value, the remaining used, pouch (b) (4) content was subtracted to get a value for the extracted amount of (b) (4) The average extraction was approximately (b) (4)

The plasma levels of salicylate in subjects in Study SM 18-01 were further analyzed in post hoc analyses. The levels of salicylic acid were used for read-across to assess the plasma levels of (b) (4). Statistically significant higher levels of salicylate $AUC_{(0-120)}$ and C_{max} were observed for Longhorn compared to ZYN (Table 14).

Table 14 ZYN Wintergreen 4.5 mg Versus Longhorn Wintergreen 18 mg for Salicylate $AUC_{(0-120)}$ and C_{max}

	Longhorn Wintergreen 18 mg (n=33)	ZYN Wintergreen 4.5 mg (n=32)	T-test P-value
$AUC_{(0-120)}$	(b) (4)		
n			
Mean (SD)			
Median (Min, Max)			
Q1; Q3 (IQR)			
C_{max}			
n			
Mean (SD)			
Median (Min, Max)			
Q1; Q3 (IQR)			

Source: Section H.3.1.2.4 Report, Table 14.8.3 and Table 14.8.4
$AUC_{(0-120)}$=area under the plasma concentration-time curve from time zero to 120 minutes; C_{max}=maximum concentration; IQR=interquartile range; Max=maximum; Min=minimum; n=number; Q=quartile; SD=standard deviation.

5.2 Pharmacodynamics

Pharmacodynamics includes the effects of the constituent on the body including physiological (ie, changes in pulse rate) and subjective effects (ie, abuse liability assessment).

5.2.1 Pulse Rate in Clinical Studies

Pulse rate is a standard assessment in nicotine research since nicotine can increase pulse rate. Therefore, pulse rate was measured as a secondary endpoint and surrogate for systemic nicotine uptake in Studies SM 17-01and SM 17-03; results are summarized by study below.

5.2.1.1 Pulse Rate: Study SM 17-01

In the 20 subjects randomized in Study SM 17-01, pulse rate was measured with an automatic device in a sitting position after 10 minutes of rest on Day 1 of each treatment for Visits 2 through 15 at before (predose) and 5, 10, 15, 30, and 60 minutes after application of the IP.

Descriptive statistics are presented in Section H.3.1.2.1 Report Body, Table 14.3-23. Individual subject data are provided in Section H.3.1.2.1 Appendix 16.2.6.

Comparison Between the Test and Reference Products

There were no statistically significant differences in change in pulse rate at the majority of time points between the test products and the reference product (General PSWL 1.0 g [8 mg]) administered during 15 minutes (Section H.3.1.2.1 Report Body, Table 14.3-24 to Table 14.3-27). Pulse rate changed over time to a similar extent in all treatment groups. The median change from baseline at 15 minutes was 7 bpm for the reference product compared to 7, 5, 10, and 9.5 bpm for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively.

There were no statistically significant differences in change in pulse rate at the majority of time points between test products and the reference product (General PSWL 1.0 [8 mg]) administered during 60 minutes, except for a significant higher pulse rate in the reference product compared to most ZYN 3 mg treatments at 10 minutes (Section H.3.1.2.1 Report Body, Table 14.3-28 to Table 14.3-35). Pulse rate increased over time to a similar extent in all treatment groups. The median change from baseline at 15 minutes was 6.5 bpm for the reference product compared to 3.5, 3, 6.5, and 8 bpm for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN Wintergreen 3 mg (nicotine), ZYN Wintergreen 3 mg (flavor), ZYN Peppermint 3 mg, and ZYN Spearmint 3 mg were 6, 3, 4, and 4.5 bpm, respectively. The median change from baseline at 60 minutes was 7 bpm for the reference product compared to 5, 2.5, 6, and 7 bpm for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN Wintergreen 3 mg (nicotine), ZYN Wintergreen 3 mg (flavor), ZYN Peppermint 3 mg, and ZYN Spearmint 3 mg were 3.5, 6, 3, and 8 bpm, respectively.

Pairwise Comparison Between the Test Products

There were no statistically significant differences between ZYN Smooth 3 mg and 6 mg compared to ZYN Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 minutes or administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-36 to Table 14.3-39).

There were no statistically significant differences between ZYN Smooth 3 mg compared to ZYN Wintergreen 3 mg, ZYN Peppermint 3 mg, or ZYN Spearmint 3 mg administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-40 to Table 14.3-42).

5.2.1.2 Pulse Rate: Study SM 17-03

In the 18 subjects randomized in Study SM 17-03, pulse rate was measured with an automatic device in a sitting position after 10 minutes of rest on Day 1 of each treatment for Visits 2 through 6 at before (predose) and 5, 10, 15, 30, and 60 minutes after application of the IP.

Descriptive data are summarized in Section H.3.1.2.2 Report Body, Table 14.3-212.

Comparison Between the Test and Reference Products

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 (Section H.3.1.2.2 Report Body, Table 14.3-202 to Table 14.3-205).

Pulse rate changed over time to a similar extent in all treatment groups. The median increase from baseline at 15 minutes was 6 bpm for the reference product (General PSWL 1.0 [8 mg]) compared to 5, 4, 11, and 8 bpm for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively.

The median increase from baseline at 60 minutes was 8 bpm for the reference product (General PSWL 1.0 [8 mg]) compared to 8, 5, 10, and 10 beats/minute for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively.

Pairwise Comparison Between the Test Products

There were no statistically significant differences in change in pulse rate between the test products at the majority of time points (Section H.3.1.2.2 Report Body, Table 14.3-84 to Table 14.3-89).

5.2.2 Subjective Effects for Abuse Liability Assessment

Subjective nicotine effect was assessed by “head buzz” (head rush, “hit,” feeling alert, overall “product strength”) as a secondary endpoint in Studies SM 17-01 and SM 17-03. In these studies, head buzz was measured using a 100-mm VAS anchored with “not at all” to ”extremely” at preset time points up to 60 minutes after study product administration (as a proxy for systemic uptake). Using VAS to measure head buzz is a standard assessment in nicotine research. Data were analyzed using the Wilcoxon signed rank sum test and Student’s t-test (paired) for within subject difference. Results are summarized by study below.

5.2.2.1 Study SM 17-01 VAS

Comparison Between the Test and Reference Products

In the nicotine extraction Study SM 17-01, there were no statistically significant differences in change in head buzz (measured by VAS) between the test products and the reference product (General PSWL 1.0 g [8 mg]) administered during 15 minutes (Section H.3.1.2.1 Report Body, Table 14.3-44 to Table 14.3-47). Head buzz changed over time to a similar extent in all treatment groups. The median change from baseline at 15 minutes was 6.5 for the reference product compared to 5.5, 5, 7, and 4 for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively.

There was a statistically significant difference at 60 minutes between ZYN Smooth 3 mg and the reference product (General PSWL 1.0 g [8 mg]) administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-48). The change in head buzz was significantly smaller compared to the reference product. There were no statistically significant differences between ZYN Smooth 6 mg, ZYN Smooth 3 mg (alternative manufacturing process), and ZYN Smooth 6 mg (alternative manufacturing process) compared to the reference product

administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-49 to Table 14.3-51).

There were statistically significant differences at 60 minutes between ZYN Wintergreen 3 mg (nicotine), ZYN Wintergreen 3 mg (flavor), ZYN Peppermint 3 mg, and ZYN Spearmint 3 mg compared to the reference product (General PSWL 1.0 g [8 mg]) administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-52, Table 14.3-53, Table 14.3-54, and Table 14.3-55, respectively). In addition, there were also statistically significant differences at time points between 10 minutes and up to 60 minutes between ZYN Wintergreen 3 mg (flavor) and ZYN Spearmint 3 mg compared to the reference product administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-53 and Table 14.3-55, respectively). The changes were significantly smaller compared to the reference product.

The median change from baseline at 15 minutes was 10.5 for the reference product (General PSWL 1.0 g [8 mg]) compared to 7.5, 3, 10.5, and 6.5 for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively. The corresponding values for ZYN Wintergreen 3 mg (nicotine), ZYN Wintergreen 3 mg (flavor), ZYN Peppermint 3 mg, and ZYN Spearmint 3 mg were 5.5, 4.5, 5.5, and 4, respectively. The median change from baseline at 60 minutes was 1.5 for the reference product compared to 0, 0, 4, and 0.5 for ZYN 3 mg, ZYN 3 mg (alternative manufacturing process), ZYN 6 mg, and ZYN 6 mg (alternative manufacturing process), respectively. The corresponding value for ZYN Wintergreen 3 mg (nicotine), ZYN Wintergreen 3 mg (flavor), ZYN Peppermint 3 mg, and ZYN Spearmint 3 mg was 0 for all treatments.

Descriptive statistics are presented in Section H.3.1.2.1 Report Body, Table 14.3-43. Individual subject data are provided in Section H.3.1.2.1 Appendix 16.2.6.

Pairwise Comparison Between the Test Products

There were no statistically significant differences between ZYN Smooth 3 mg and 6 mg compared to ZYN Smooth 3 mg and 6 mg (alternative manufacturing process), respectively, administered during 15 minutes or 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-56 to Table 14.3-59).

There were no statistically significant differences between ZYN Smooth 3 mg compared to ZYN Wintergreen 3 mg or ZYN Peppermint 3 mg administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-60 and Table 14.3-61, respectively). There was a statistically significant difference in change in head buzz at 60 minutes between ZYN Smooth 3 mg and ZYN Spearmint 3 mg administered during 60 minutes (Section H.3.1.2.1 Report Body, Table 14.3-62). The change was significantly larger for ZYN Smooth 3 mg compared to ZYN Spearmint 3 mg; however, the change was only 1 mm, which is considered not clinically relevant.

5.2.2.2 Study SM 17-03 VAS

Comparison Between the Test and Reference Products

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 (Section H.3.1.2.2 Report Body, Table 14.3-213 to Table 14.3-216.

There was an increase in head buzz in all treatment groups compared to baseline. The increase was larger for the reference product (General PSWL 1.0 g [8 mg]) than those for the ZYN products (3 mg and 6 mg) at all time points. The median change from baseline at 15 minutes 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 minutes 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 Section H.3.1.2.2 Report Body, Table 14.3-223.

Pairwise Comparison Between the Test Products

There were no statistically significant differences in change in head buzz (measured by VAS) between the test products at the majority of time points (Section H.3.1.2.2 Report Body, Table 14.3-217 to Table 14.3-222).

5.3 Nicotine Dependence

Similar to the concept of a “continuum of risk” for different tobacco products (Levy et al 2006; Sweanor et al 2007), there may also exist a “continuum of dependence” (Fagerström and Eissenberg 2012; Tiffany et al 2004) that would range from high in cigarettes to low (if any) in nicotine replacement therapy (NRT) (West et al 2000). The dependence for Swedish snus, and therefore also ZYN, is probably intermediate between the two (Fagerström and Eissenberg 2012).

Nicotine dependence “in users of smokeless tobacco might have different characteristics compared with the nicotine dependence of smokers” (Fagerström et al 2010). For example, users of Swedish snus might “have been less resistant to cessation than corresponding populations of smokers, who have long been under pressure to quit” (Fagerström et al 2010). A study of discordant twins suggests that the nature of the dependence in users of Swedish snus is different from that in cigarette users (Edwards et al 2011).

In cigarette smokers, the transfer of nicotine from the inhaled smoke to the brain has been reported to be extremely rapid (Benowitz 2008; Hukkanen et al 2005), reflecting the blood flow directly from the lungs to the brain. In users of smokeless tobacco products, nicotine absorption occurs orally, producing much slower delivery to the brain (Benowitz 1997). Nonetheless, nicotine supplementation in the form of NRT is associated with a modest increase of cessation rates among smokers motivated to quit. It has been hypothesized that the relatively low level of efficacy observed in controlled clinical trials and population studies is related to the nicotine delivery profile of currently available NRT products, which may produce insufficient reductions of craving and urges to smoke.

In a study of oral mucosal changes among users of smokeless tobacco, the authors found that the average steady-state saliva cotinine concentration was about 300 ng/mL both for users of loose Swedish snus (n=22) and users of pouched Swedish snus (n=23); levels were similar to those reported among smokers (Andersson et al 1994). A randomized, open-label, cross-over clinical trial including 63 smokers found that during a two-week test period, Swedish snus was superior to a 4-mg piece of nicotine gum in terms of reducing urges to smoke compared to baseline, although the decrease in the total craving score was not statistically significant for either product (Caldwell et al 2010). Both Swedish snus and nicotine gum enabled subjects to reduce their smoking significantly compared to baseline. At the end of the test period, participants were asked to rank their preferred purpose for using the products if they could use them long term. Subjects could choose from three possible uses: “short term to quit smoking,” “to reduce smoking,” or “long term instead of smoking.” Swedish snus were ranked higher than the gum in all three dimensions; with a statistically significant difference for the “quit” and “reduce” dimensions.

The rates of absorption of nicotine from different products in two studies reported by Holm et al 1992 examining nicotine intake in users of loose Swedish snus are shown in Figure 5. The Swedish snus users and cigarette smokers reported similar levels of subjective dependence on tobacco. The more rapid nicotine delivery from Swedish snus compared to the NRT products (gum and patch) may help to explain why many smokers in Sweden and Norway have quit cigarettes completely by switching to Swedish snus.

As demonstrated in the clinical studies conducted with ZYN and snus for this PMTA, ZYN delivers nicotine at similar rates as snus (Section 5.1.4.5); therefore, it is presumed that it would also fall between combustible cigarettes and NRT in the “continuum of dependence.”

Figure 5 Nicotine Intake in Users of Loose Swedish Snus

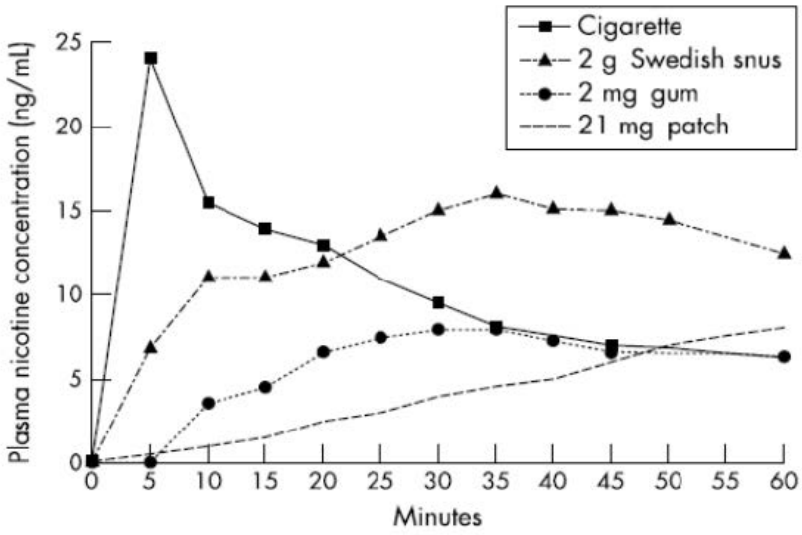


Figure 1 Venous blood concentrations in nanograms of nicotine per millilitre (ng/ml) of plasma as a function of time for various nicotine delivery systems; all plasma nicotine concentrations have been reconfigured such that the pre-absorption level starts at 0 ng/ml (that is, to take out the baseline differences). Cigarette, and 2 mg nicotine gum, adapted from Russell *et al*,[24] and 21 mg patch adapted from Stratton *et al*,[3] page 100. Swedish snus plasma nicotine concentrations in 10 Swedish snus users from a single 2 g pinch of loose snus adapted from Holm *et al*.[21]

Source: Foulds et al 2003

6 SAFETY FROM CLINICAL CONSUMER STUDIES

To assess the safety and tolerability of ZYN, the following safety-related assessments were collected in the studies conducted for this PMTA:

- Treatment-emergent AEs were collected in all four clinical studies as secondary endpoints as well as in the consumer research Study (b) (4) (Patterns of Use) (Section 6.1).
- Oral safety as measured by dental plaque acidogenicity, changes in oral microflora, changes in plaque amount, and the appearance and number of oral mucosal lesions was assessed in Study SM 17-02 (Section 6.2).

6.1 Adverse Events Reported in the Clinical and Consumer Research Studies

There were no deaths, other SAEs, or discontinuations due to AEs reported in any of the studies.

Across the four clinical studies, all AEs were mild or moderate, and the majority were in the GI Disorders System Organ Class (SOC), which includes oral-related AEs (eg, dry mouth, gingival pain) (Section H.3.1.2.1 Report Body, Table 12.2-2; Section H.3.1.3.1 Report Body, Table 12.1-2 and Table 14.4-2; Section H.3.1.2.2 Report Body, Table 12.2-2; Section H.3.1.2.3 Report Body, Table 12.1-1 and Table 12.2-1).

Overall, few oral-related AEs were reported in the clinical studies (Appendix 1). The most common AE, and the only one reported in more than one study, was dry mouth (GI Disorders SOC). All of these oral-related AEs were assessed as possibly or probably related to IP by the Investigator, with the exception of oropharyngeal pain (Study SM 17-03) and lip pain (Study SM 17-02).

In the consumer perception Study (b) (4) (Patterns of Use), unsolicited AEs or product complaints spontaneously reported by study participants were collected. AEs were reported by two participants; both were non-serious:

- One participant reported runny nose, grogginess, sinus infection, and exhaustion.
- One participant reported flu, head cold, cough, sore throat, congestion, and chills.

6.2 Oral Safety Study SM 17-02

In Study SM 17-02, oral safety assessments included the following:

- Dental plaque acidogenicity as measured by the microtouch method as described in Section H.3.1.3.1 Report Body, Section 9.5.2.2
- Plaque amount assessed with a plaque score as described in Section H.3.1.3.1 Report Body, Section 9.5.2.3
- Oral microflora as measured from pooled plaque samples collected by a sterile toothpick as described in Section H.3.1.3.1 Report Body, Section 9.5.2.4
- Examination of the oral cavity performed according to Axell et al 1976 as described in Section H.3.1.3.1 Report Body, Section 9.5.2.1

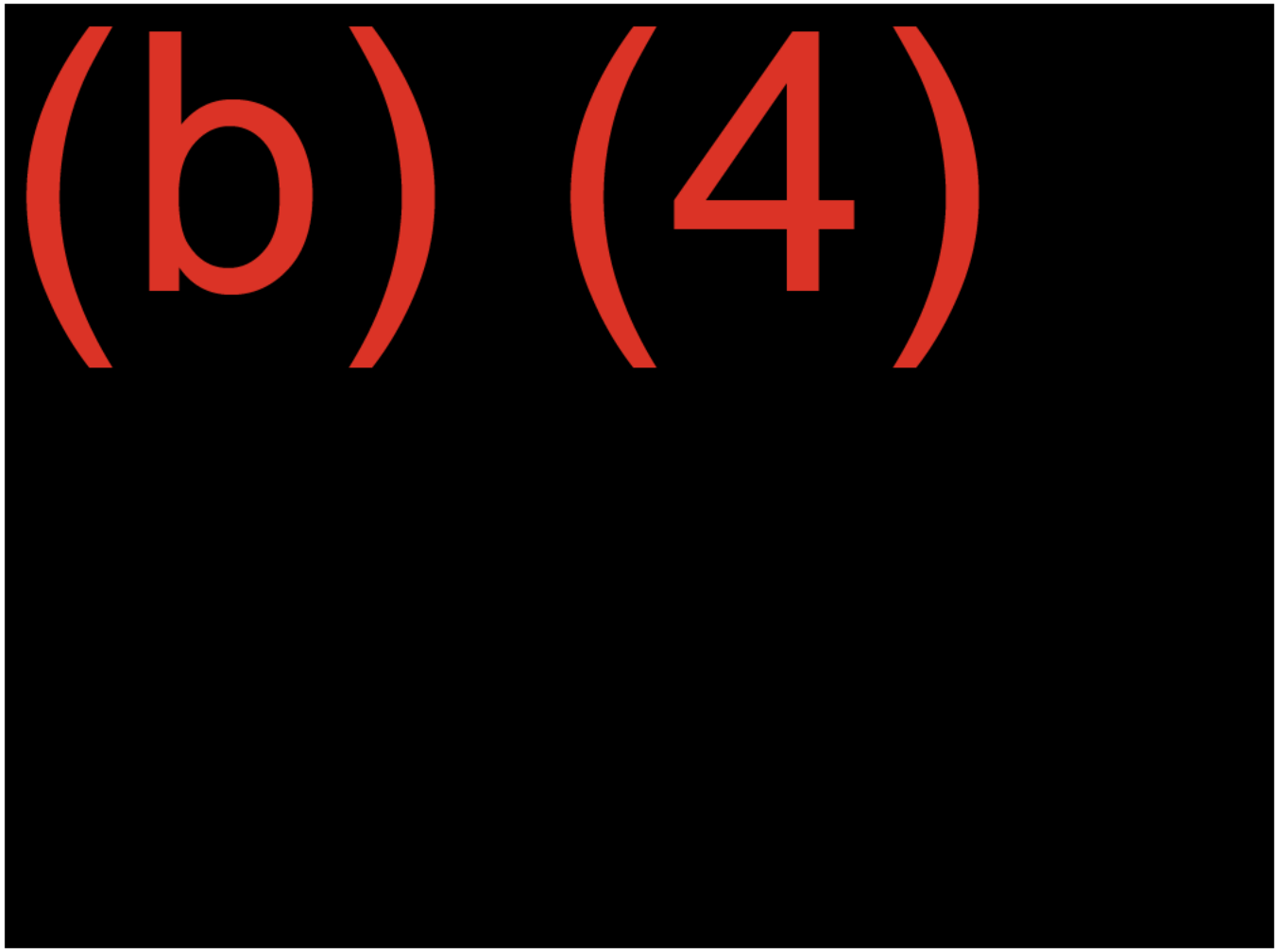
- Salivary factors pH and flow rate (unstimulated and stimulated) as measured from saliva collected into a beaker as described in Section H.3.1.3.1 Report Body, Section 9.5.2.5

6.2.1 Dental Plaque Acidogenicity (Primary Endpoint)

6.2.1.1 Part 1: Dental Plaque Acidogenicity After Short-Term Exposure

In Part 1 of Study SM 17-02, plaque pH was measured during short-term (60 minutes) exposure to ZYN Smooth 3 mg and ZYN Peppermint 3 mg. The change in plaque pH was also measured before and during 60 minutes after rinsing for 1 minute with a solution of either 10% sucrose (positive control) or 10% xylitol (negative control). Mean values of dental plaque pH by time point are shown in Figure 6. For sucrose, the pH fell below the levels associated with an increased risk for demineralization of dentin (pH <6.2) and enamel (pH <5.5). In contrast, after administration of a 10% xylitol solution (negative control), the plaque pH remained essentially unchanged compared to the value before administration. During administration of ZYN Smooth 3 mg and ZYN Peppermint 3 mg, the plaque pH value was slightly higher (approximately 0.2 units) compared to the pre-administration value. There were no statistically significant differences between the two ZYN products. The AUC below both of the reference limits (pH 5.5 and 6.2) was significantly larger for sucrose than for any of the other three treatments (for which the AUC values were all zero). Dental plaque acidogenicity between-group comparisons are presented in Section H.3.1.3.1 Report Body, Table 14.3-3. These results show that single-dose administrations of the two ZYN products do not promote plaque acidogenesis.

Figure 6 Mean Dental Plaque Acidogenicity (pH) vs Time (Per Protocol Set) (Study SM 17-02 Part 1)

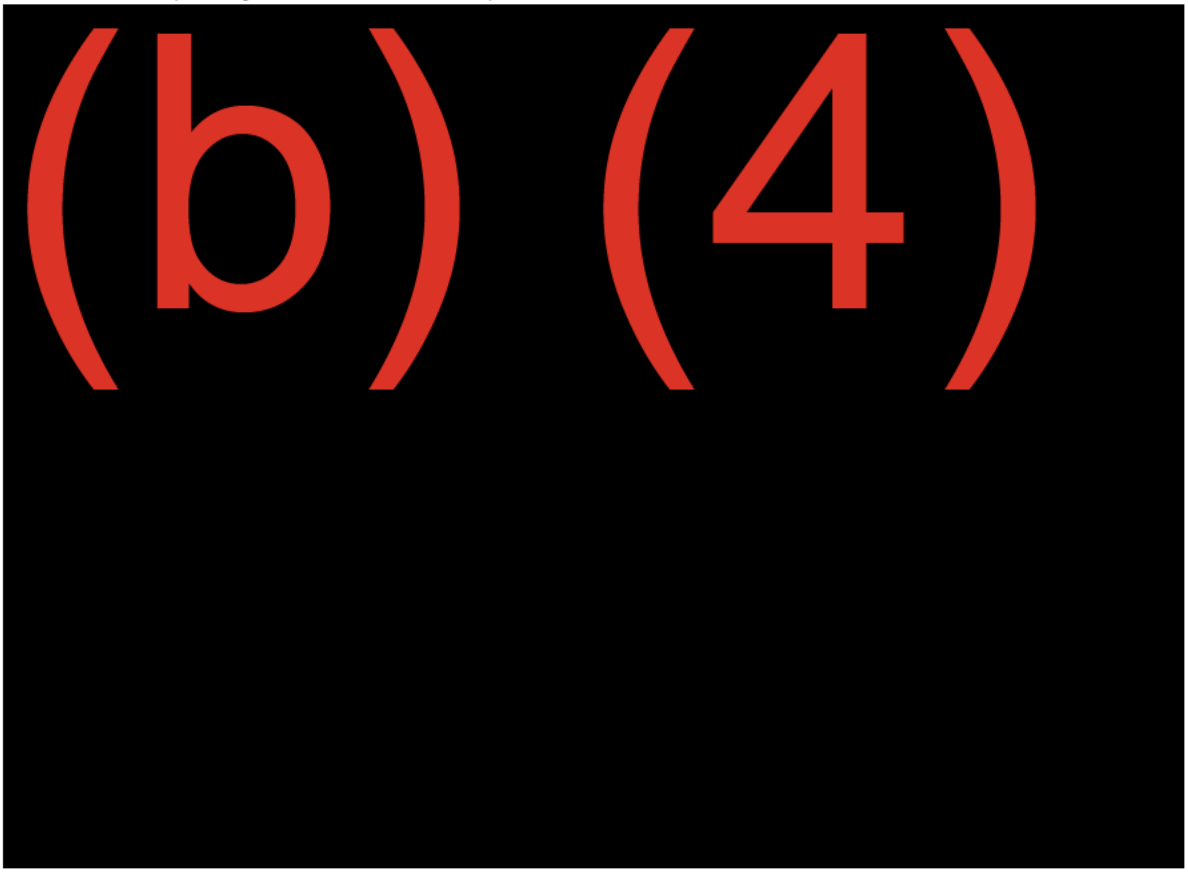


Source: Section H.3.1.3.1 Report Body, Figure 11.2-1

6.2.1.2 Part 2: Dental Plaque Acidogenicity After 6 Weeks of Use

In Part 2 of Study SM 17-02, dental plaque acidogenicity was evaluated by measuring the plaque pH before and up to 60 minutes after rinsing the mouth with a 10% sucrose solution. Acidogenicity was determined at the Screening visit and after 2, 4, and 6 weeks (Visits 3, 4, and 5, respectively) of *ad libitum* administration of ZYN pouches. Mean values of dental plaque pH during the acidogenicity measurements by time point are shown in Figure 7. The pH drop caused by exposure to sucrose (ie, the acidogenicity) was largest at the Screening visit and became progressively smaller during the time of the study. The largest negative change in pH value was significantly larger at the Screening visit compared to at the visits during the study. Furthermore, the AUCs below pH 6.2 and pH 5.5 were significantly larger at the Screening visit than at the visits during the study. The results show that acidogenicity was decreased during the study compared to at the Screening visit. Dental plaque acidogenicity between-group comparisons are presented in Section H.3.1.3.1 Report Body, Table 14.3-5.

Figure 7 Mean Dental Plaque Acidogenicity (pH) vs Time (Per Protocol Set) (Study SM 17-02 Part 2)



Source: Section H.3.1.3.1 Report Body, Figure 11.2-2

6.2.2 Plaque Amount (Part 2: Secondary Endpoint)

In Part 2 of Study SM 17-02, plaque amount measurements were performed at the Screening visit and at 2, 4, and 6 weeks (Visits 3, 4, and 5, respectively). There were only a few occasional statistically significant changes from baseline in plaque amount at Visits 3, 4, and 5 for the females, males, and all subjects (Section H.3.1.3.1 Report Body, Table 14.3-11). For example, the total index (for the males and all subjects) was lower during the study compared to baseline and the total index for the site mesio-buccal at Visit 3 (two weeks), and Visit 5 (six weeks) was higher compared to baseline.

6.2.3 Oral Microflora (Part 2: Secondary Endpoint)

In Part 2 of Study SM 17-02, oral microflora measurements were performed at the Screening visit and at 2, 4, and 6 weeks (Visits 3, 4, and 5, respectively). There were statistically significant changes from baseline for *S. mutans* (both actual and log values) at Visits 4 and 5 for all subjects and the female subjects, but not for the male subjects (Section H.3.1.3.1 Report Body, Table 14.3-12). However, it is worth noting that at baseline, the observed number of *S. mutans* were considerably lower for the female subgroup compared to the male subgroup.

The number at Visit 4 (four weeks) and Visit 5 (six weeks) was higher compared to baseline. There were no statistically significant changes from baseline for Lactobacilli during the study.

6.2.4 Oral Mucosal Lesions (Part 2: Secondary Endpoint)

In Part 2 of Study SM 17-02, the oral cavity was examined for mucosal lesions at the Screening visit and at 2, 4, and 6 weeks (Visits 3, 4, and 5, respectively). There was no indication of changes in the incidence of gingival retraction during the study; it varied between 54% and 57% during the study (Section H.3.1.3.1 Report Body, Table 14.3-13).

The number of subjects with lesions and the degree of lesions changed during the study. The number of subjects with no lesions increased from 9% at screening to 30% at Visit 5 (six weeks), and the number of subjects with lesions of degree 3 and 4 decreased (the number of subjects with lesions of degree 1 and 2 increased). The number of subjects with lesions in the mucosa at placement of the pouch decreased from 90% to 70%.

There was a statistically significant change in the degree of lesions at the placement of the pouch between Visit 3 (two weeks), Visit 4 (four weeks), and Visit 5 (six weeks) compared to baseline for the subgroups and in total (Section H.3.1.3.1 Report Body, Table 14.3-14). The degree of lesions was lower at Visit 3 (two weeks), Visit 4 (four weeks), and Visit 5 (six weeks) compared to baseline. There was a statistically significant correlation between change in oral mucosal lesions and percentage of ZYN products used for all visits except the female subjects at Visit 4 (four weeks) (Section H.3.1.3.1 Report Body, Table 14.1-11, Table 14.1-12, Table 14.3-15, and Figure 14.3-1 to Figure 14.3-9).

7 CONSUMER USE AND RISK PERCEPTION

Swedish Match has conducted two consumer research studies in the US for this PMTA:

- A Likelihood of Use study (Study (b) (4) among both users and non-users of TNP
- A Patterns of Use study (Study (b) (4) among users of ZYN and a group of non-users

Both studies were designed based on the FDA draft guidance for industry entitled Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, dated May 2016, and feedback was received from FDA (Section A.4 FDA Meeting Minutes, 12 October 2017 – TC0002533). Since ZYN has been marketed in the US since 2014, Swedish Match was able to recruit actual US consumers for the Patterns of Use study. Efforts were made to oversample people who use TNP of legal age to 24 years of age as well as TNP users with intention to quit for the Likelihood of Use study. In the Patterns of Use study, ZYN users and non-users were enrolled if they were at least the minimum legal age for TNP use per local state requirements. Youth under the legal age limit were not included in the consumer research studies as it was not considered ethical.

Key results from these two studies are summarized by topic in this section. All study results can be found in:

- Likelihood of Use study (Study (b) (4) : Section H.3.1.1.2 Report Body, Section 13
- Patterns of Use study (Study (b) (4) : Section H.3.1.1.1 Report Body, Section 13

There is no literature on ZYN use. Since ZYN is a smokeless, pouched product like snus (as described in Section 1), a literature search was performed on the likelihood of snus use since it is the most closely related product in the smokeless category. Results from this literature search is used as supportive data in this section.

Swedish Match also collects unsolicited data from consumers from the call center (1-855-YOUR-ZYN) and the website (https://www.zyn.com/us/en/). A report of contact center activity from October 2017 through October 2019 is provided in Section H.1.3.1 Consumer Reported Complaints; slide 7 includes a list of contacts related to improper use of ZYN, and slide 8 includes a list of health-related issues potentially related to ZYN use.

7.1 Prevalence of Use of ZYN

7.1.1 Sales Data

Swedish Match utilizes Nielsen as its source of retail scanner sales data. In comparison to distributor-measured sales:

- Nielsen data represent 19% of stores carrying ZYN.
- Nielsen data represent 25% of volume sales.

Therefore, because Nielsen provides actual consumer takeaway and is representative of the total market, Nielsen data is provided in this PMTA.

It is important to note that ZYN was only available in retail stores in 13 states (the product was available nationwide via internet sales) in the Western US from August to March 2019. In April 2019, ZYN became available in retail stores in all 50 states.

Figure 8 provides store count and unit sales by month from August 2016 to October 2019.

Figure 8 ZYN Store Count and Unit Sales by Month From August 2016 to October 2019

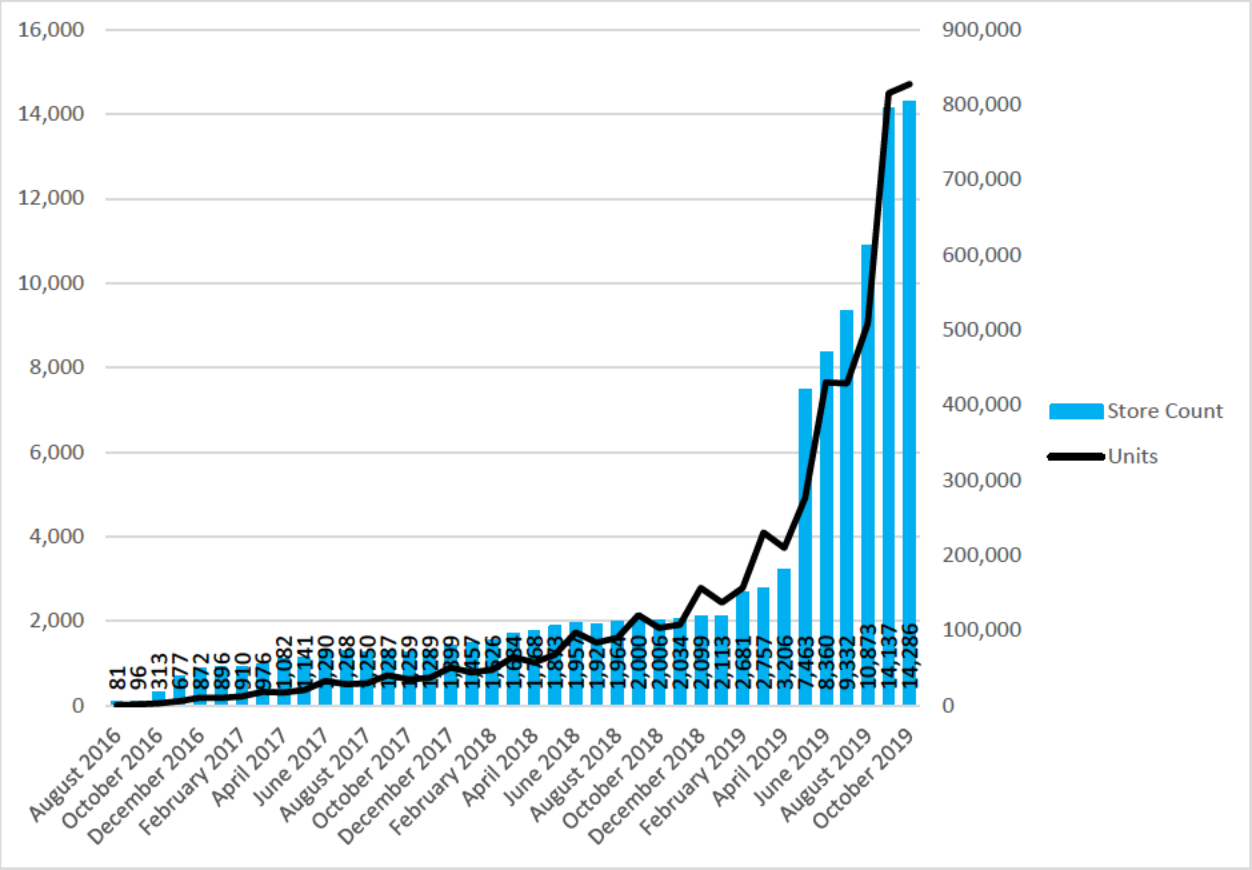
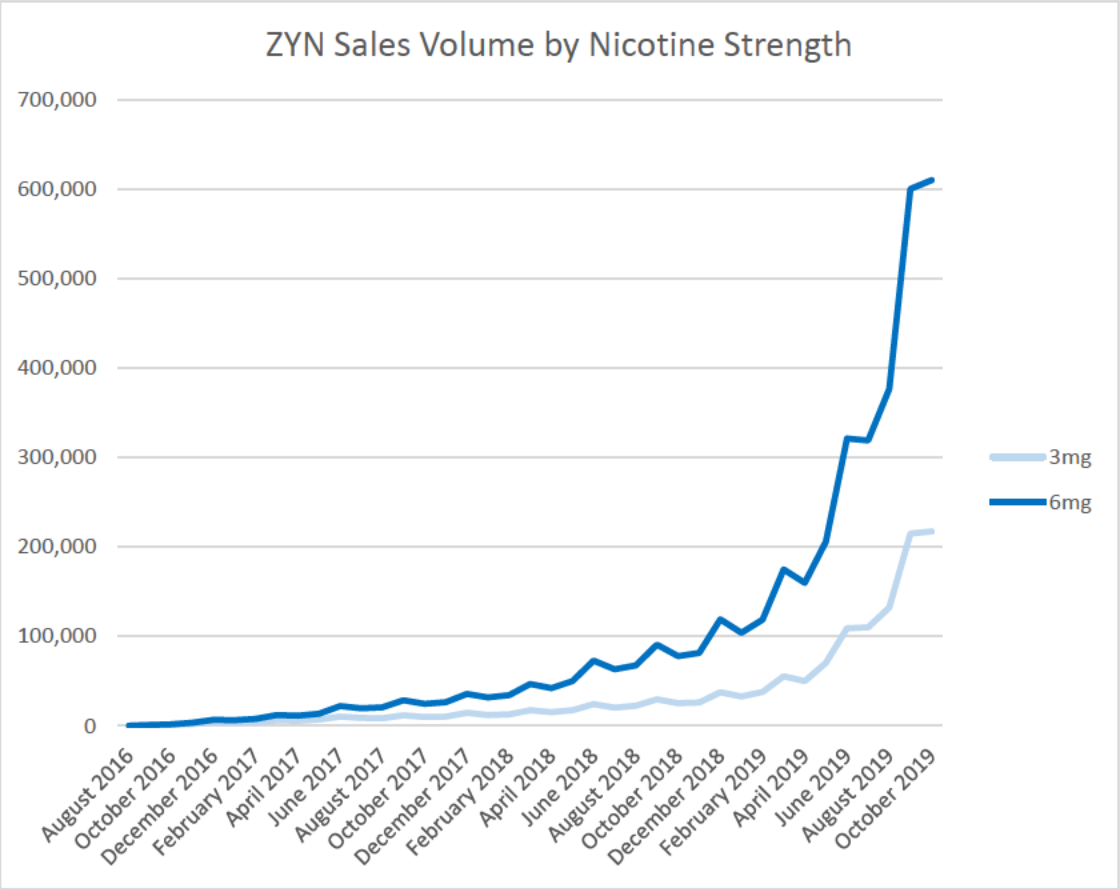


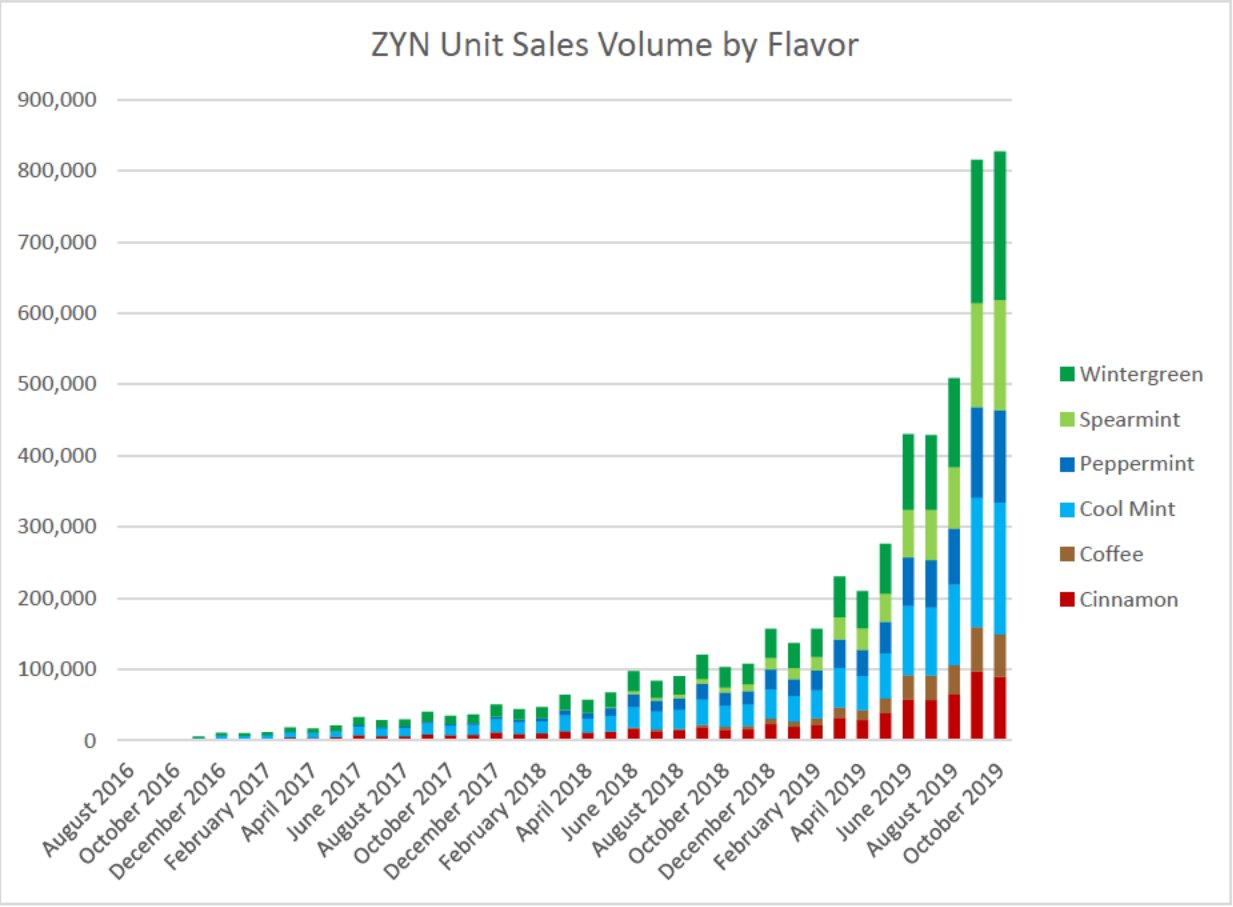
Figure 9 provides sales volume, separating out 3 mg and 6 mg nicotine strengths. Consistent with consumer-stated behavior and distributor data, the 6 mg nicotine strength comprises the majority of ZYN sales. In October 2019, the 6 mg strength comprised 74% of ZYN sales.

Figure 9 ZYN Sales Volume by Nicotine Strength From August 2016 to October 2019



Lastly, Figure 10 provides sales volume, separating out the six available flavors of ZYN. Consistent with consumer stated behavior and distributor data, mint flavors comprise the majority of ZYN sales. In October 2019, the four mint flavors comprised 82% of ZYN sales.

Figure 10 ZYN Unit Sales Volume by Flavor From August 2016 to October 2019



7.1.2 Socio-demographic Characteristics From Consumer Research

The Retrospective Study of Study (b) (4) (Patterns of Use) recruited (b) (4) ZYN users from the 11 states (Arizona, California, Colorado, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, and Wyoming) where ZYN is sold. Socio-demographic characteristics of this cohort are shown in Table 15. (b) (4)

[redacted]

Table 15 Socio-demographic Characteristics of ZYN Users in Study (b) (4) (Patterns of Use)

Characteristic	ZYN Users (b) (4)
(b) (4)	

Characteristic	ZYN Users (b) (4)
(b) (4)	

Source: Section H.3.1.1.1 Report Body, Table 3
GED=General Educational Development.

7.2 User Topography

Over the (b) (4), observational, Prospective Study period in the consumer research Study (b) (4) (Patterns of Use), ZYN users reported consistent use of an average of approximately (b) (4) ZYN pouches a day (Section H.3.1.1.1 Report Body, Table 12).

User topography (ie, how the individual users consume the product) was assessed by compliance with ZYN usage instructions over the last seven days in the ZYN users cohort in Study (b) (4) (Patterns of Use). Results are summarized in Table 16. In general, ZYN users showed compliance with suggested directions for product use. For the following two items, compliance was low:

- Duration of usage: Usage instructions suggest discarding a ZYN pouch after 60 minutes in one's mouth. Only (b) (4) of users reported they never use a pouch for more than 60 minutes, per instruction, whereas (b) (4) reported that they always do.
- Placement of ZYN pouch in the mouth: (b) (4) of users responded that they always place the pouch between their gum and upper lip, per instruction, whereas (b) (4) reported that they never do.

Table 16 Primary Objective 3: Compliance With ZYN Usage Instructions (ZYN Users, (b) (4) (Study (b) (4) – Retrospective)

	n (%) (95% CI)
Placed a ZYN pouch between my gum and upper lip	
Always (%)	(b) (4)
Sometimes (%)	
Never (%)	
Don't know (%)	
Decline to answer (%)	
Used one ZYN pouch at a time	
Always (%)	
Sometimes (%)	
Never (%)	
Don't know (%)	
Decline to answer (%)	

	n (%) (95% CI)
Used one ZYN pouch for more than 60 minutes	(b) (4)
Always (%)	
Sometimes (%)	
Never (%)	
Don't know (%)	
Decline to answer (%)	
Cut the ZYN pouch open and used the pouch contents	
Always (%)	
Sometimes (%)	
Never (%)	
Don't know (%)	
Decline to answer (%)	

Source: Section H.3.1.1.1 Report Body, Table 8
CI=confidence interval; NA=not applicable.

7.3 Factors Influencing Patterns of Use

7.3.1 Reasons for Using ZYN

Reasons for ZYN use were assessed during the (b) (4) Prospective Study of Study (b) (4) (Patterns of Use) among ZYN users (b) (4) using one item in the biweekly survey assessing why respondents had used ZYN. Respondents were allowed to select more than one reason from the choices listed in Table 17.

Table 17 Reasons for Use Choices in Biweekly Survey (Study (b) (4)

To help me reduce my cigarette smoking	To add variety to the products I use
To help me quit smoking cigarettes	Comes in flavors I like
To help me reduce my use of tobacco products other than cigarettes	Does not cause me to smell like smoke/tobacco
To help me quit using tobacco products other than cigarettes	Comes in two different levels of nicotine strength
To use in environments where other tobacco/nicotine products are not considered appropriate (eg, church)	Less harmful for those around me than cigarettes
To use in environments where other tobacco/nicotine products are not allowed (e.g., airplane, etc.)	More acceptable to non-tobacco users
Less harmful to my health than cigarettes	No one can tell when I am using it
Less harmful to my health than other tobacco products, excluding cigarettes	I was just curious to see what it was like
To avoid spitting as required with other products	Ease of use
None of the above	Recommended by person who works in the store where I buy my TNP
Decline to answer	Don't know

Source: Section H.3.1.1.1 Report Body, Section 9.4.1.2
TNP=tobacco/nicotine product.

The most commonly reported reasons (≥50% of respondents) for using ZYN at (b) (4) were the following (Section H.3.1.1.1 Report Body, Table 18):

- To help reduce cigarette smoking ((b) (4)
- Ease of use (b) (4)
- No one can tell when I am using it (b) (4)
- To help quit smoking cigarettes (b) (4)
- To use in environments where other TNP are not considered appropriate (eg, church, etc) (b) (4)
- To use in environments where other TNPs are not allowed (eg, airplane, etc.) (b) (4)
- Less harmful to my health than cigarettes (b) (4)
- Does not cause me to smell like smoke/tobacco (b) (4)

- Comes in flavors I like (b) (4)
- To avoid spitting as required with other products (b) (4)

7.3.2 Consumer Preferences and ZYN Brand Appeal

7.3.2.1 ZYN Users

The consumer research Study (b) (4) (Patterns of Use) evaluated the product preferences of the ZYN user cohort and collected the following data:

- Flavor of ZYN preference
- Nicotine strength of ZYN preference
- Duration of ZYN use
- Proportion of ZYN usage with 6 mg nicotine strength

Results are shown in Table 18. The majority of ZYN users had been using ZYN for 6 months or less, and (b) (4) reported having used ZYN for 3 to 4 months. ZYN users rated Wintergreen and Cool Mint as most popular (b) (4) Coffee was the least popular flavor. The strongest nicotine strength (6 mg) was most common, used by (b) (4) of the cohort, with (b) (4) of respondents reporting they used 6 mg all the time.

Table 18 ZYN Product Preferences in Retrospective Study (Study (b) (4)

		ZYN users (b) (4)	
		Column Valid N %	Count
Flavor of ZYN	Cinnamon	(b) (4)	
	Coffee		
	Cool Mint		
	Peppermint		
	Spearmint		
	Wintergreen		
	Don't know		
Nicotine strength of ZYN	3 mg		
	6 mg		
	Don't know		

		ZYN users (b) (4)	
		Column Valid N %	Count
Duration of using ZYN	Less than 1 month ago	(b) (4)	
	1-2 months ago		
	3-4 months ago		
	5-6 months ago		
	7-8 months ago		
	9-10 months ago		
	11-12 months ago		
	13-18 months ago		
	19-23 months ago		
	24 months ago		
Proportion of ZYN usage with 6 mg nicotine strength in past 30 days	All (100%) of my ZYN usage		
	About 3/4 (75%) of my ZYN usage		
	Half (50%) of my ZYN usage		
	About 1/4 (25%) of my ZYN usage		
	I did not use the 6 mg strength in the past 30 days		

Source: Section H.3.1.1.1 Report Body, Table 20

7.3.2.2 ZYN Non-users

In addition, in Study (b) (4) (Likelihood of Use), the appeal of the ZYN brand and product attributes, including the overall brand, packaging, the pouches themselves, the child-safety lid, and flavor variety were collected as primary objective 2. In general, TNP users, compared with TNP non-users, considered the ZYN brand to be more appealing (Section H.3.1.1.2 Report Body, Section 13.3.2 and Table 17 and Section H.3.1.1.2 Attachment 17.1 Descriptive Tables 1-14, Table 10). About one-third to one-half of TNP users considered the ZYN brand, overall packaging, flavor variety, and pouches to be moderately to very appealing. In contrast, most TNP non-users did not find the ZYN brand, product, packaging, and flavor variety appealing at all. The child-safety lid was the most appealing attribute among both TNP and non-TNP users.

7.3.3 Flavorings Appeal

ZYN is currently marketed in the US in 6 different flavors (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, and Cinnamon), and the mint flavors comprised (b) (4) of ZYN sales (Figure 10). This PMTA also includes four additional flavors: Citrus Smooth Chill and Fresh Swedish Match has chosen flavors for ZYN that appeal more toward adult consumers and avoid appealing to youth.

The consumer research studies evaluated flavor preferences and variety in current ZYN users as well as current TNP and non-TNP users. In the Retrospective Study phase of Study (b) (4) (Patterns of Use Study), ZYN users rated Wintergreen and Cool Mint as most popular ((b) (4) respectively; Table 18), which is consistent with sales data. Coffee

was the least popular flavor (b) (4) In Study (b) (4) (Likelihood of Use), approximately half of current TNP users considered the flavor variety to be moderately to very appealing, whereas the majority of current TNP non-users (never and former) did not find the flavor variety appealing at all (Section H.3.1.1.2 Attachment 17.1 Descriptive Tables 1-14, Table 10).

7.3.4 Youth Use and Appeal

ZYN is only for adults 21 years and older who currently use tobacco or nicotine.

7.3.4.1 Marketing and Code of Conduct

As part of our marketing and ethical code of conduct, Swedish Match takes proactive measures to ensure all marketing communication for ZYN is targeted to adults who are current tobacco consumers. Swedish Match believes in responsibility above all to prevent youth access and youth exposure of brand communication whether it be labeling, promotions, advertising, or social media. Examples of how our marketing efforts are tailored to prevent youth access and exposure are as follows:

- Swedish Match has a partnership with (b) (4), which includes a secondary layer of brand safety monitoring and blocking across all marketing campaigns and efforts.
- The ZYN website (https://www.zyn.com/us/en/) is age-restricted to self-identified adults who must register and undergo a strict age verification process through a third party as opposed to simply asking for current age (see Figure 11, Figure 12, and Figure 13 for screenshots).
- ZYN adheres to a strict marketing code of conduct, which goes beyond what the law requires, including the following:
  - Advertisements are made only in media where audience is ≥85%+ adult.
  - Models used in advertising must be and appear at least 25 years of age.
  - No professional athletes will be used for product endorsements.
  - No entertainer who appeals primarily to youth shall be used in any advertising.
  - Social media (eg, Facebook) is restricted to consumers over 21 years of age (see Figure 14 for screenshots of ZYN Facebook page notification).

Figure 11: Screenshot of ZYN Website Home Page- Age Restriction Notification

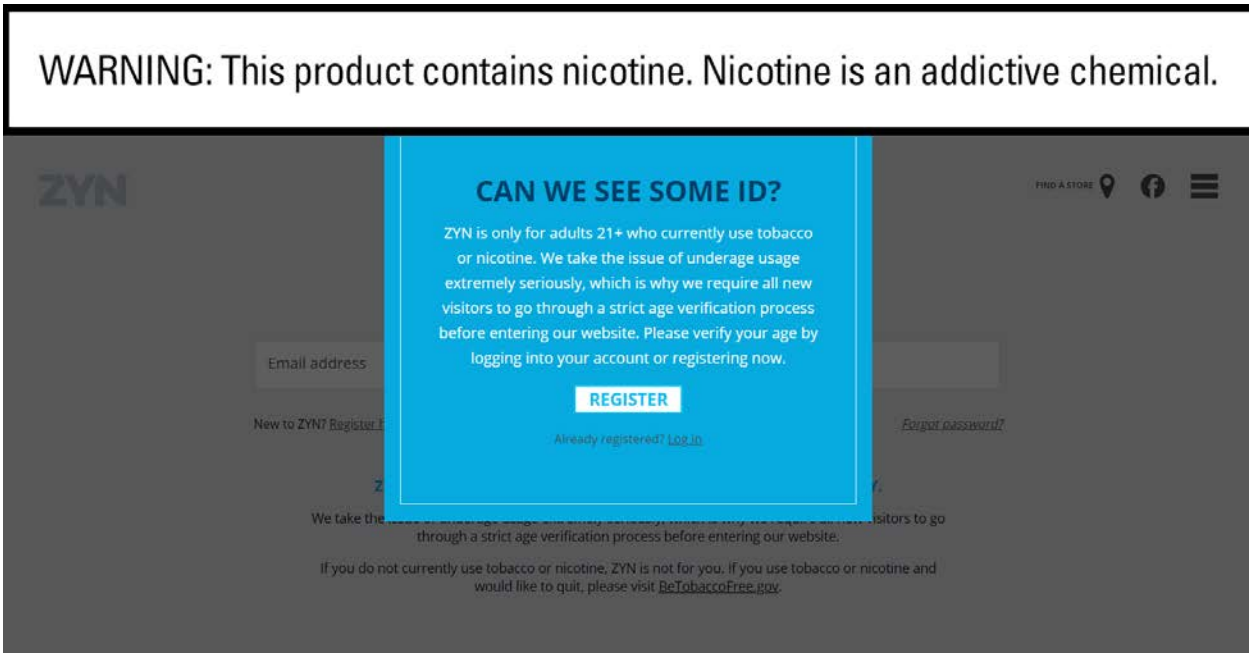


Figure 12: Screenshot of ZYN Website Home Page- Login

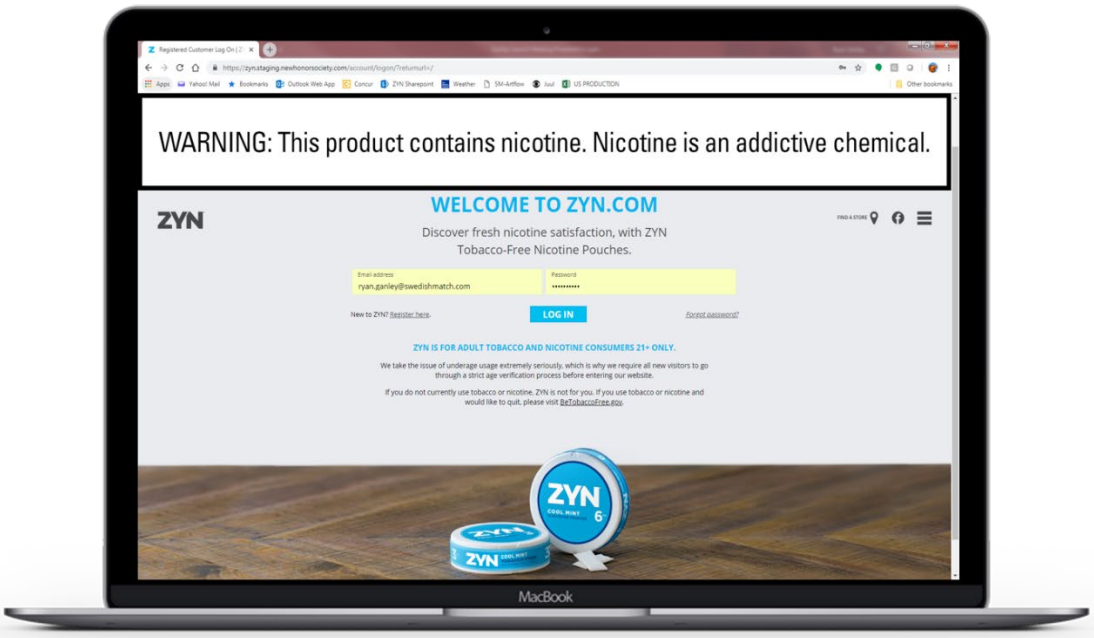


Figure 13: Screenshot of ZYN Website Home Page- Login (Zoomed In)

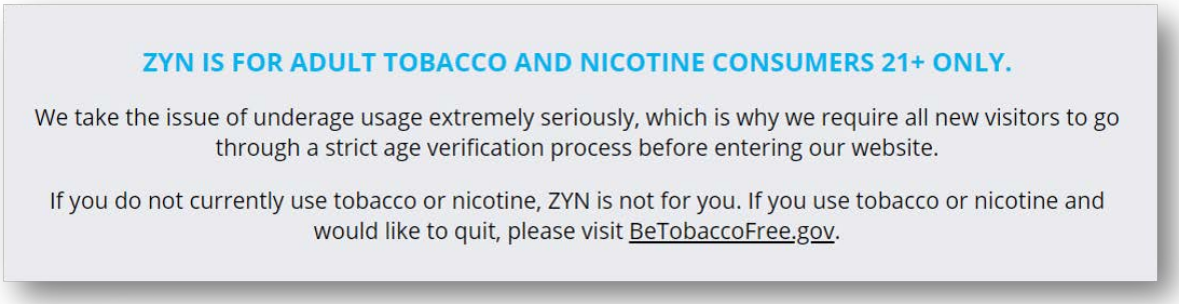
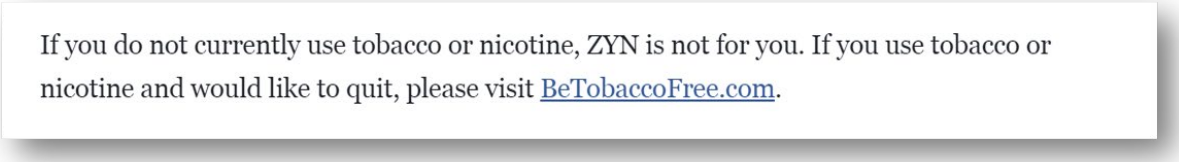


Figure 14: Screenshots of ZYN Facebook Page Notification



7.3.4.2 Youth Use

There are no published data with youth use and ZYN. The use of smokeless tobacco and snus, which is similar to the ZYN product, is currently low among US youth. The 2018 National Youth Tobacco Survey reported that smokeless tobacco accounted for 5.9% and 1.8% of current tobacco use by high school and middle school students, respectively, which were significant declines from 2011 to 2018 (Gentzke et al 2019).

The FDA has observed that flavors have been shown to play a role in the product's attractiveness to youth (FDA Draft Guidance 2019). As noted in the FDA Modifications to Compliance Policy for Certain Deemed Tobacco Products Draft Guidance for Industry (March 2019) Section VI on page 19, "current data demonstrate that minors prefer alternative flavors, such as fruit, over mint- and menthol-flavored ENDS products, and it is possible that mint- and menthol-flavored ENDS products may be important to some adults who seek to use specific ENDS products to cease

combustible tobacco product use." Therefore, Swedish Match has chosen flavors for ZYN that appeal more toward adult consumers (eg, Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Coffee, Cinnamon, Smooth, Chill, and Fresh) and avoided youth-appealing flavors.

In the US consumer research studies conducted for this PMTA, youth under the legal age limit were not included as it was not considered ethical.

7.4 ZYN Label Comprehension

In the consumer research Likelihood of Use Study (b) (4), comprehension of the ZYN label was assessed by using one item measuring comprehension of the various pieces of information presented. The multiple-choice response options included the following:

- ZYN contains nicotine.
- The packaging label includes a warning that nicotine is an addictive chemical.
- ZYN comes in the form of chewing gum.
- ZYN comes in a total of three flavors.
- ZYN comes in both 3 mg of nicotine and 6 mg of nicotine varieties.
- Don't know.
- Decline to answer.

About (b) (4) of all respondents (b) (4) responded that the ZYN product contains nicotine, and (b) (4) recalled the packaging label's warning that nicotine is an addictive chemical (Section H.3.1.1.2 Report Body, Table 11 and Section H.3.1.1.2 Attachment 17.1 Descriptive Tables 1-14, Table 9). Less than (b) (4) of respondents answered that ZYN comes in the form of chewing gum, and (b) (4) thought it came in a total of three flavors. Approximately half of all respondents answered that ZYN comes in both 3 mg and 6 mg nicotine varieties. However, more current TNP users (b) (4) answered that ZYN came in both 3 mg and 6 mg nicotine varieties. Overall, these measures demonstrated that the majority of respondents comprehended the ZYN product label.

7.5 Patterns of Use

Patterns of TNP and ZYN use were assessed in the retrospective and prospective parts of Study (b) (4). Key results are summarized in this section.

7.5.1 Dual Use

7.5.1.1 Study (b) (4) – Retrospective Study

TNP usage in the last 30 days for each cohort in the Retrospective Study for ZYN users and non-users is shown in Table 19. ZYN users reported low rates of using other TNP products (ie, dual use) either every day or some days. The most commonly (>10%) reported TNP products also

used by ZYN users were moist snuff, cigarettes, e-cigarettes, and snus. Of ZYN users enrolled in this study, (b) (4) reportedly smoked cigarettes (every day or some days) over the past 30 days and (b) (4) reportedly smoked every day.

Table 19 Reported TNP Use in the Last 30 Days (Primary Objective 1: Study (b) (4) – Retrospective)

	ZYN Users (b) (4) n (%) (95% CI)	**ZYN Non-users (b) (4) n (%) (95% CI)**
Reported cigarette use, N[a]	(b) (4)	
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		
Reported e-cigarette use, N[a]		
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		
Reported moist snuff use, N[a]		
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		

	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
Decline to answer (%)	(b) (4)	
Reported chewing tobacco use, N[a]		
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		
Reported snus use, N[a]		
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		
Reported ZYN or other nicotine pouch use, N[a]		
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		

	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
Reported aids to help stop smoking use, N[a]	(b) (4)	
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		
Reported cigars, cigarillos, filtered cigars filled with tobacco use, N[a]		
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		
Reported pipe tobacco use, N[a]		
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		

	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
Reported hookah or water pipe tobacco use, N[a]	(b) (4)	
Every day (%)		
Some days (%)		
Not at all (%)		
Don't know (%)		
Decline to answer (%)		

Source: Section H.3.1.1.1 Report Body, Table 4
CI=confidence interval; n=number of subjects who reported; N=total number; NA=not applicable; TNP=tobacco/nicotine product.
Column percentages are out of the total population for the cohort not the N value of each question.
[a] Number of non-missing responses.

In ZYN users, TNP use reported in the last 30 days compared to weeks prior to using ZYN in the Retrospective Study is shown in Table 20. The number of ZYN users who reported to never have used a non-ZYN TNP and the number of users reported not using TNP during the weeks prior to using ZYN were very low (b) (4) respectively). Prior to using ZYN, 82.4% of ZYN users had previously used two or more TNP. The most common combination of TNP use was moist snuff and snus (b) (4) followed by moist snuff and cigarettes (b) (4) Of particular note, only (b) (4) of ZYN users in this study reported that they had never used a non-ZYN TNP product prior to using ZYN.

Table 20 Combinations of TNP Use During the Weeks Prior to Using ZYN (ZYN Users, (b) (4)) (Primary Objective 2: Study (b) (4) – Retrospective)

	(b) (4)
TNP ever use	
Never used a non-ZYN TNP	
TNP use during the weeks prior to using ZYN	
# of people not using TNP	
Using one TNP (Mono-users)	
Exclusive Moist Snuff Users	
Exclusive Smokers	
Using 2+ TNP	
Using exactly 2 TNP	

	(b) (4)
Using 3+ TNP	
Most common pairs prior to using ZYN	
Using Moist Snuff + Snus	
Using Moist Snuff + Cigarette	
Using Moist Snuff + Chewing Tobacco	
Using Moist Snuff + Cigars	

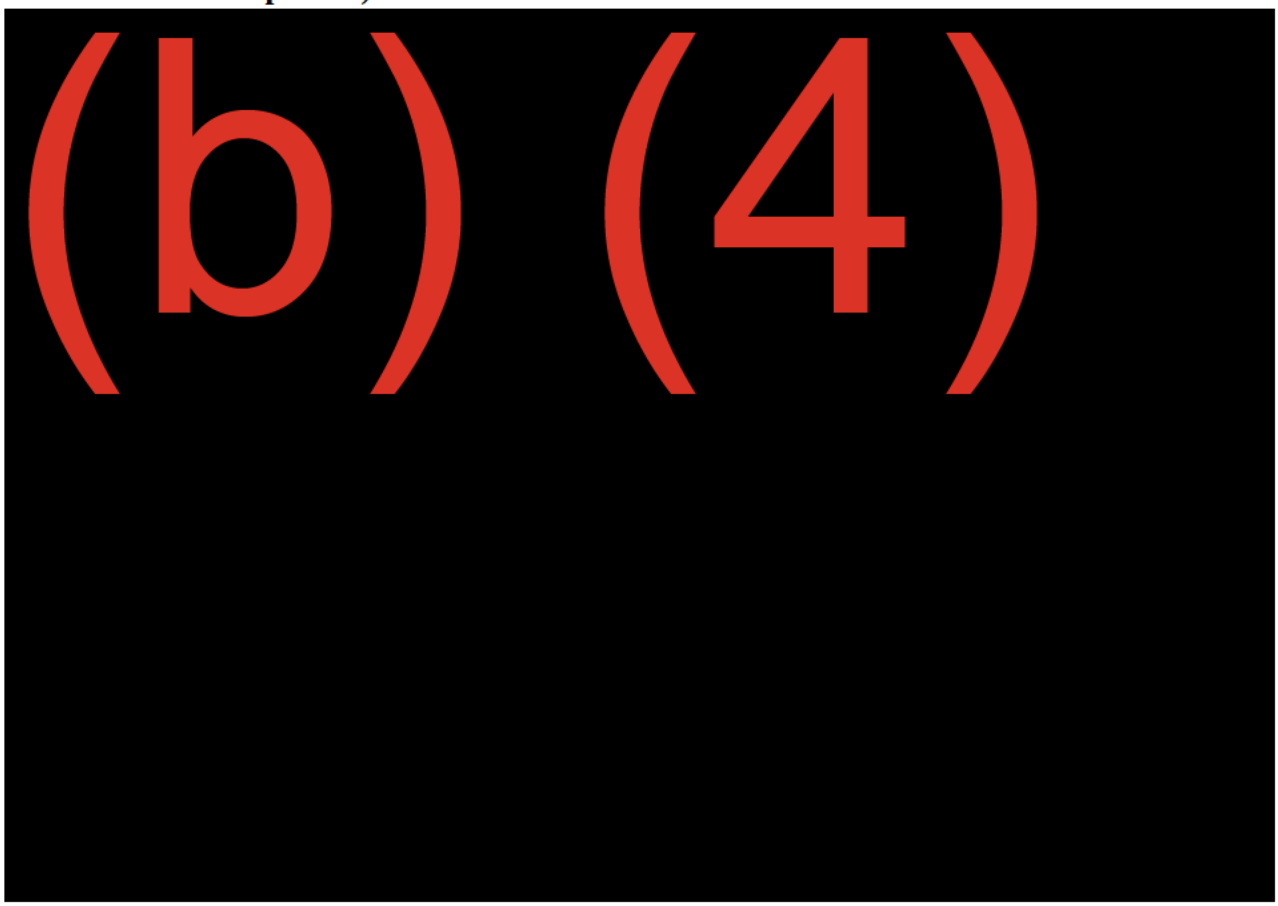
Source: Section H.3.1.1.1 Report Body, Table 6a
TNP=tobacco/nicotine product.

7.5.1.2 Study (b) (4) – Prospective Study

In the (b) (4) observational, Prospective Study, daily TNP patterns of use, including reasons for ZYN use, were assessed. See Section H.3.1.1.1 Report Body, Table 12 through Table 18 and Figure 1 through Figure 3 for the daily patterns of use of TNP among ZYN users and non-users. All results can be found in Section H.3.1.1.1 Report Body, Section 13.4.5. Key takeaways are as follows:

- The number of respondents who smoked cigarettes and/or used moist snuff every day or some days (defined as at least 1 day a week) decreased for ZYN users from week 1 (b) (4)
- The percentage of respondents that reported using only ZYN increased throughout the study from week 1 to week 10, and the percentage that used other TNP decreased (Figure 15 and Section H.3.1.1.1 Report Body, Table 15 and Figure 4).

Figure 15 TNP Patterns of Use Among ZYN Users - Percent of ZYN Users Using ZYN With Other TNP (Secondary Objective 5: Study (b) (4) – Prospective)



Source: Section H.3.1.1.1 Report Body, Figure 3
TNP=tobacco/nicotine product.

7.5.2 Intention to Quit TNP or Switch from TNP to ZYN

7.5.2.1 Study (b) (4) – Retrospective Study

Intention to quit TNP based on the MTSS for each cohort in the Retrospective Study is shown in Table 21. Across all types of TNP, with the exception of ZYN, ZYN users expressed higher intent to quit versus ZYN non-users.

Table 21 Intention to Quit TNP Based on the MTSS (Primary Objective 1: Study (b) (4) – Retrospective)

	ZYN Users (b) (4)	ZYN Non-users (b) (4)
Intention to quit cigarettes, N[a]	(b) (4)	
Mean±SD		
(95% CI)		
Intention to quit e-cigarettes, N[a]		
Mean±SD		
(95% CI)		
Intention to quit moist snuff, N[a]		
Mean±SD		
(95% CI)		
Intention to quit chewing tobacco, N[a]		
Mean±SD		
(95% CI)		
Intention to quit snus, N[a]		
Mean±SD		
(95% CI)		
Intention to quit ZYN or other nicotine pouches, N[a]		
Mean±SD		
(95% CI)		
Intention to quit aids to help stop smoking, N[a]		
Mean±SD		
(95% CI)		
Intention to quit cigars, cigarillos, filtered cigars filled with tobacco, N[a]		
Mean±SD		
(95% CI)		
Intention to quit pipe tobacco, N[a]		
Mean±SD		
(95% CI)		

	ZYN Users (b) (4)	ZYN Non-users (b) (4)
Intention to quit hookah or water pipe tobacco, N[a]	(b) (4)	
Mean±SD		
(95% CI)		

Source: Section H.3.1.1.1 Report Body, Table 5
CI=confidence interval; MTSS=Motivation to Stop Scale; SD=standard deviation; TNP=tobacco/nicotine product.
The MTSS has seven response options ranging from 1=I don't want to stop smoking to 7=I REALLY want to stop smoking and intend to in the next month. A "Don't know" response is also available. The MTSS was validated to predict quit attempts for cigarette usage but has been adapted to measure quit intention for other TNP.
[a] Number of non-missing responses.

7.5.2.2 Study (b) (4) – Prospective Study

In the (b) (4) Prospective Study, quitting was defined as recording zero TNP use of any kind in weeks (b) (4). Complete substitution was defined as starting the Prospective Study using ZYN and another TNP but recording use of only ZYN in weeks (b) (4). By weeks (b) (4) of ZYN users reported completely substituting ZYN in place of other TNP (Table 22). Additionally, a small proportion of ZYN users and non-users reported quitting all TNP by weeks (b) (4)

Table 22 Quitting All TNP Use or Completely Substituting Other TNP for ZYN at the End of the Prospective Study (Secondary Objective 6: Study (b) (4) – Prospective)

	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
Quitting all TNP as of weeks (b) (4) (for 14+ days)	(b) (4)	
Completely substituting ZYN in place of other TNP		

Source: Section H.3.1.1.1 Report Body, Table 19
CI=confidence interval; NA=not applicable; TNP=tobacco/nicotine product.

7.6 Likelihood of Use

The likelihood of ZYN use was assessed in never TNP users, former TNP users, and current TNP users in Study (b) (4). Key results are summarized in this section.

7.6.1 Likelihood That Non-users Will Initiate Use of ZYN

7.6.1.1 Study (b) (4) (Likelihood of Use)

The current likelihood to buy a TNP among never TNP users (Cohorts 1 and 2) was measured pre-exposure to the ZYN stimuli in Study (b) (4) and was assessed using an 11-point

Juster scale. Overall, never TNP users were unlikely to initiate TNPs prior to being exposed to the ZYN stimuli (Table 23). After exposure to the ZYN stimuli, the likelihood to buy ZYN among never TNP users was similarly low for cohorts of legal age to age 24 years (b) (4) and >24 years (b) (4)

Table 23 Likelihood That Never Users Will Buy TNP - Mean Juster Scores (Primary Objective 1: Study (b) (4)

	Cohort 1: Never Tobacco Users From Legal Age to 24 Years of Age (b) (4)	Cohort 2: Never Tobacco Users > 24 Years of Age (b) (4)
Future likelihood to buy ZYN[a]	(b) (4)	
Mean±SD		
(95% CI)		
Current likelihood to buy cigarettes[b]		
Mean±SD		
(95% CI)		
Current likelihood to buy moist snuff[b]		
Mean±SD		
(95% CI)		
Current likelihood to buy snus[b]		
Mean±SD		
(95% CI)		

Source: Section H.3.1.1.2 Report Body, Table 12
CI=confidence interval; n=number of respondents; SD=standard deviation; TNP=tobacco/nicotine products.
[a] Measured post-exposure to ZYN stimuli.
[b] Measured pre-exposure to ZYN stimuli.

7.6.1.2 From the Literature

The likelihood that non-users will initiate use was also examined from the available scientific evidence in the literature with the use of Swedish snus, a relevant comparator product, since there is no literature on ZYN. From the literature, snus uptake was more frequent among younger populations, and males were more likely to initiate tobacco to use with snus (Section I.1 Use Behavior Update Report, Section 3.1). Studies also reported an increase in snus uptake in recent years, regardless of age or gender. Furthermore, the proportion of snus users who had never smoked has increased and more women are taking up snus compared to previous decades.

In addition, as noted in the General Snus FDA PMTA TPL Review 2015, FDA does not anticipate that based on the "marketing of the proposed products, as described in the PMTAs, there is a low likelihood of non-user uptake of these products." Since General Snus and ZYN are marketed by the same company, then the likelihood of non-user uptake of ZYN is also low.

7.6.2 Likelihood That Non-users Who Adopt ZYN Will Switch to Other TNP That Present Higher Levels of Individual Health Risk

This was examined from the available scientific evidence in the literature with the use of Swedish snus, a relevant comparator product, since there is no literature on ZYN. From the literature, the proportion of snus users who picked up smoking habits among snus users was small compared to the proportion of smokers who then added snus use as a habit (Section I.1 Use Behavior Update Report, Section 3.2). Furthermore, those who started daily tobacco use with snus had a lower probability of acquiring a daily smoking habit compared to those who did not initiate daily tobacco use with snus, based on data from the nationally representative longitudinal study "Your Country and Your Life" 2003-2011 in Sweden (Ramström et al 2016).

7.6.3 Likelihood That Former Users of TNP Will Reinitiate Use With ZYN

7.6.3.1 Study (b) (4) (Likelihood of Use)

The current likelihood to buy a TNP among former TNP users (Cohort 3) was measured pre-exposure to the ZYN stimuli in Study (b) (4) and was assessed using an 11-point Juster scale. Overall, former TNP users were unlikely to initiate or reinitiate TNPs prior to being exposed to the ZYN stimuli (Table 24). After exposure to the ZYN stimuli, the likelihood to buy ZYN among former tobacco users from legal age and older was low (b) (4) (Table 24) and lower than never TNP users (Table 23).

Table 24 Likelihood That Former TNP Users Will Buy TNP - Mean Juster Scores (Primary Objective 1: Study SMNA 17-11ZYN)

	Cohort 3: Former Tobacco Users From Legal Age and Older (b) (4)
Future likelihood to buy ZYN[a]	(b) (4)
Mean±SD	
(95% CI)	
Current likelihood to buy cigarettes[b]	
Mean±SD	
(95% CI)	
Current likelihood to buy moist snuff[b]	
Mean±SD	
(95% CI)	
Current likelihood to buy snus[b]	
Mean±SD	
(95% CI)	

Source: Section H.3.1.1.2 Report Body, Table 12
CI=confidence interval; n=number of respondents; SD=standard deviation; TNP=tobacco/nicotine products.
[a] Measured post-exposure to ZYN stimuli.
[b] Measured pre-exposure to ZYN stimuli.

7.6.3.2 From the Literature

The likelihood that former TNP users will reinitiate use was also examined from the available scientific evidence in the literature with the use of Swedish snus, a relevant comparator product, since there is no literature on ZYN. There is little information in the literature; however, a downward trend in the prevalence of former snus users who currently smoked was found (Section I.1 Use Behavior Update Report, Section 3.3). Data from Scandinavian cohorts have shown that being a former smoker is common among snus users (Lund et al 2010; Lund et al 2011; SCENIHR 2008; Scheffels et al 2012), and there is some suggestion that relapse among former smoking snus users are low (5% during 10 years) (Lundqvist et al 2009).

7.6.4 Likelihood to Buy ZYN among TNP Users

Among TNP user groups (Cohorts 4, 5, 6, and 7) in Study (b) (4), the likelihood to buy ZYN after exposure to the ZYN stimuli ranged from a mean Juster score of (b) (4) (Table 25). After exposure to the ZYN stimuli, cigarette smokers intending to quit were more likely to buy ZYN than cigarette smokers not intending to quit.

Table 25 Future Intention to Buy ZYN Among TNP Users – Mean Juster Scores (Primary Objective 1: Study (b) (4)

Future Likelihood to Buy ZYN	Cohort 4: Current Cigarette Smokers With Intention to Quit From Legal Age to 24 Years of Age (b) (4)	Cohort 5: Current Cigarette Smokers With Intention to Quit > 24 Years of Age (b) (4)	Cohort 6: Current Cigarette Smokers Without Intention to Quit Legal Age and Older (b) (4)	Cohort 7: Current Tobacco Users (Excluding Cigarettes) From Legal Age and Older (b) (4)
Mean±SD	(b) (4)			
(95% CI)				

Source: Section H.3.1.1.2 Report Body, Table 13
CI=confidence interval; n=number of respondents; SD=standard deviation; TNP=tobacco/nicotine products.

7.6.5 Likelihood That Tobacco Users Who Start Using ZYN Will Switch to or Switch Back to Other Tobacco Products That Present Higher Levels of Individual Risk

This was examined from the available scientific evidence in the literature with the use of Swedish snus, a relevant comparator product, since there is no literature on ZYN. Based upon longitudinal and cross-sectional studies that examined snus use and the risk of future smoking in several populations in Sweden and other Scandinavian countries, there is little evidence that prior snus use leads to daily cigarette smoking among adults, and only a small percentage of smokers made the transition to smoking from daily snus use (Section I.1 Use Behavior Update Report, Section 2.3). In addition in Study (b) (4), the ZYN users over time reported reduced use of TNP products other than ZYN.

7.6.6 Likelihood That Consumers Will Use ZYN in Conjunction With Other TNP (Dual Use)

This was examined from the available scientific evidence in the literature with the use of Swedish snus, a relevant comparator product, since there is no literature on ZYN. Dual use of snus and cigarettes has been reported at low rates in the literature (from approximately 2% to 10%) (Section I.1 Use Behavior Update Report, Section 2.4). Women were less likely than men to use snus and other TNP. Dual use was commonly cited as part of an attempt to quit smoking, and the majority of dual users started tobacco use with cigarettes.

7.6.7 Likelihood That ZYN Users Who May Have Otherwise Quit Using Tobacco Products Will Instead Use ZYN

This was examined from the available scientific evidence in the literature with the use of Swedish snus, a relevant comparator product, since there is no literature on ZYN. From the literature, Swedish snus is commonly and intentionally used as a smoking cessation aid in Sweden and other countries (Section I.1 Use Behavior Update Report, Section 2.5).

In a long-term Swedish study (from 2003 to 2011) of over 60,000 adults aged 18 to 79 years, snus was shown to be an important contributor to improve public health (Ramström et al 2016). Among those who tried to quit smoking without the aid of snus, only half were successful. In addition, approximately one-third of secondary snus users eventually quit all snus use and became entirely tobacco free, refuting the common assumption that snus use would entail lifelong nicotine dependence.

7.6.8 Likelihood That Consumers Will Switch to ZYN Instead of Using an FDA-approved Tobacco-Cessation Product

This was examined from the available scientific evidence in the literature with the use of Swedish snus, a relevant comparator product, since there is no literature on ZYN. Even though snus and ZYN are not marketed as cessation products, snus use is commonly used as an effective smoking cessation aid, with increasing prevalence during recent years especially in Europe (Section I.1 Use Behavior Update Report, Section 2.5). Former or current smokers frequently use snus, and it is more common among male tobacco users than females. One large set of longitudinal data of Swedes reported that over three-quarters of smokers who picked up snus as a secondary daily tobacco product completely quit smoking. Among those who tried to quit smoking without the aid of snus, only half were successful (Ramström and Foulds 2006).

7.7 Perceptions of Health Risk

7.7.1 Perceptions of Absolute Health Risk

Perceptions of absolute health risk were assessed for four health conditions (b) (4)) as secondary objectives in Study (b) (4) (Likelihood of Use) and the Retrospective Study of Study (b) (4) (Patterns of Use). Key results are summarized in this section.

7.7.1.1 Study (b) (4)

Prior to exposure of the ZYN stimuli in Study (b) (4) perceptions of the absolute health risk of smoking cigarettes daily and never having used TNPs were assessed for four health

conditions with response options ranging from a very low to a very high risk of developing these conditions. Across the seven cohorts, the majority of respondents perceived that a person who smoked only cigarettes daily and used no other TNP had a high to very high absolute risk of developing a health condition (Section H.3.1.1.2 Report Body, Table 18). Overall, TNP non-users and cigarette smokers with intention to quit perceived higher absolute risks (eg, respondents answered "high" to "very high") of developing a health condition for daily cigarette smoking compared with current tobacco users (excluding cigarettes) and cigarette smokers without intention to quit. Across all cohorts, (b) (4) of respondents perceived a very low to low absolute risk of developing a health condition for a person who has never used TNPs (Section H.3.1.1.2 Report Body, Table 19).

Post-exposure to ZYN stimuli, perceptions of absolute health risk of the daily use of ZYN and no other TNP was assessed for each of the four health conditions. Across the seven cohorts, approximately (b) (4) of respondents perceived a moderate to high chance of developing any of the four health conditions with daily ZYN use (Table 26). Less than (b) (4) of respondents across cohorts perceived a very high absolute risk with ZYN. Across the four health conditions, the perceptions of absolute risk due to the daily use of ZYN were similar across TNP never-user age groups. In general, TNP users perceived lower health risks associated with the ZYN product compared with TNP non-users. Cigarette smokers perceived low to moderate absolute health risk, across conditions, of daily use of ZYN. For cigarette users intending to quit, a larger proportion of the legal to 24 years of age population (b) (4) perceived moderate risks compared with the population >24 years of age (b) (4)

When looking across all absolute risk metrics, a consistent pattern evolved. Respondents found that cigarettes presented the greatest risk of harm. Usage of ZYN was associated with some risk of health conditions, but a lower rate than cigarettes. Never using TNP was generally deemed to carry the lowest risk.

Table 26 Perceptions of Absolute Risk Associated With Using Only ZYN Daily (Secondary Objective 1: Study (b) (4)

	1. Never Tobacco Users From Legal Age to 24 Years of Age (b) (4)	2. Never Tobacco Users Older Than 24 Years of Age (b) (4)	3. Former Tobacco Users From Legal Age and Older (b) (4)	4. Current Cigarette Smokers With Intention to Quit From Legal Age to 24 Years of Age (b) (4)	5. Current Cigarette Smokers With intention Io Quit Older Than 24 Years of Age (b) (4)	6. Current Cigarette Smokers Without Intention to Quit Legal Age and Older (b) (4)	7. Current Tobacco Users (Excluding Cigarettes) From Legal Age and Older (b) (4)
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
(b) (4)	(b) (4)						
Very low chance (%)							
Low chance (%)							
Moderate chance (%)							
High chance (%)							
Very high chance (%)							
Don't know (%)							
Decline to answer (%)							

	1. Never Tobacco Users From Legal Age to 24 Years of Age (b) (4)	2. Never Tobacco Users Older Than 24 Years of Age (b) (4)	3. Former Tobacco Users From Legal Age and Older (b) (4)	4. Current Cigarette Smokers With Intention to Quit From Legal Age to 24 Years of Age (b) (4)	5. Current Cigarette Smokers With intention Io Quit Older Than 24 Years of Age (b) (4)	6. Current Cigarette Smokers Without Intention to Quit Legal Age and Older (b) (4)	7. Current Tobacco Users (Excluding Cigarettes) From Legal Age and Older (b) (4)
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
(b) (4)							
Very low chance (%)	(b) (4)						
Low chance (%)							
Moderate chance (%)							
High chance (%)							
Very high chance (%)							
Don't know (%)							
Decline to answer (%)							

	1. Never Tobacco Users From Legal Age to 24 Years of Age (b) (4)	2. Never Tobacco Users Older Than 24 Years of Age (b) (4)	3. Former Tobacco Users From Legal Age and Older (b) (4)	4. Current Cigarette Smokers With Intention to Quit From Legal Age to 24 Years of Age (b) (4)	5. Current Cigarette Smokers With intention Io Quit Older Than 24 Years of Age (b) (4)	6. Current Cigarette Smokers Without Intention to Quit Legal Age and Older (b) (4)	7. Current Tobacco Users (Excluding Cigarettes) From Legal Age and Older (b) (4)
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
(b) (4)							
Very low chance (%)	(b) (4)						
Low chance (%)							
Moderate chance (%)							
High chance (%)							
Very high chance (%)							
Don't know (%)							
Decline to answer (%)							

	1. Never Tobacco Users From Legal Age to 24 Years of Age (b) (4)	2. Never Tobacco Users Older Than 24 Years of Age (b) (4)	3. Former Tobacco Users From Legal Age and Older (b) (4)	4. Current Cigarette Smokers With Intention to Quit From Legal Age to 24 Years of Age (b) (4)	5. Current Cigarette Smokers With intention Io Quit Older Than 24 Years of Age (b) (4)	6. Current Cigarette Smokers Without Intention to Quit Legal Age and Older (b) (4)	7. Current Tobacco Users (Excluding Cigarettes) From Legal Age and Older (b) (4)
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
(b) (4)							
Very low chance (%)							
Low chance (%)							
Moderate chance (%)							
High chance (%)							
Very high chance (%)							
Don't know (%)							
Decline to answer (%)							

(b) (4)

Source: Section H.3.1.1.2 Repo
CI=confidence interval; n=number of respondents; N=total number; NA=not applicable; TNP=tobacco/nicotine products.

7.7.1.2 Study (b) (4) – Retrospective Study

In the Retrospective Study of Study (b) (4), perceptions of absolute risk of the four health conditions were assessed among two cohorts: ZYN users and ZYN non-users. Results are shown in Table 27. When evaluating the perception of absolute risk of TNP types, both ZYN users and non-users conveyed understanding of a continuum of risk when considering use of no TNP, ZYN (useonly), and cigarettes. Specifically, respondents in both cohorts perceived the absence of any TNP use as having minimal health risk (very low to low) across all four health conditions assessed. Usage of ZYN was perceived as having low-to-moderate health risk (ZYN users only) by the largest percentage of respondents across the four conditions investigated. Cigarette smoking was perceived to have a moderate to very high risk across the four conditions for both cohorts.

Table 27 Perceptions of Absolute Risk (Secondary Objective 1: Study (b) (4) – Retrospective)

	Risk to a Person Who Has Never Used Any TNP		Risk to a Person Who Uses ZYN Everyday but Uses No Other TNP	Risk to a Person Who Smokes Cigarettes Everyday but Uses No Other TNP	
	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
(b) (4)					
Very low chance (%)	(b) (4)				
Low chance (%)					
Moderate chance (%)					
High chance (%)					
Very high chance (%)					
Don't know (%)					
Decline to answer (%)					

	Risk to a Person Who Has Never Used Any TNP		Risk to a Person Who Uses ZYN Everyday but Uses No Other TNP	Risk to a Person Who Smokes Cigarettes Everyday but Uses No Other TNP	
	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
(b) (4)					
Very low chance (%)					
Low chance (%)					
Moderate chance (%)					
High chance (%)					
Very high chance (%)					
Don't know (%)					
Decline to answer (%)					

	Risk to a Person Who Has Never Used Any TNP		Risk to a Person Who Uses ZYN Everyday but Uses No Other TNP	Risk to a Person Who Smokes Cigarettes Everyday but Uses No Other TNP	
	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
(b) (4)					
Very low chance (%)	(b) (4)				
Low chance (%)					
Moderate chance (%)					
High chance (%)					
Very high chance (%)					
Don't know (%)					
Decline to answer (%)					

	Risk to a Person Who Has Never Used Any TNP		Risk to a Person Who Uses ZYN Everyday but Uses No Other TNP	Risk to a Person Who Smokes Cigarettes Everyday but Uses No Other TNP	
	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Users (b) (4) n (%) (95% CI)	ZYN Non-users (b) (4) n (%) (95% CI)
(b) (4)					
Very low chance (%)	(b) (4)				
Low chance (%)					
Moderate chance (%)					
High chance (%)					
Very high chance (%)					
Don't know (%)					
Decline to answer (%)					

Source: Section H.3.1.1.1 Report Body, Table 8
CI=confidence interval; n=number of respondents; N=total number; NA=not applicable; TNP=tobacco/nicotine product.

7.7.2 Perceptions of Relative Health Risk

Perceptions of relative health risk were also assessed for the same four health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems) as secondary objectives in Study (b) (4) (Likelihood of Use) (all seven cohorts [(never, former, and current TNP users]) and the Retrospective Study of Study (b) (4) (Patterns of Use) (ZYN users only). Key results are summarized in this section by comparison of ZYN to cigarettes, other TNP, dual use, stop smoking aids, quitting all TNP, or never using any TNP.

7.7.2.1 Perceptions of Relative Health Risk of ZYN Compared to Cigarettes

In Study (b) (4), across all seven cohorts (never, former, and current TNP users), approximately (b) (4) of respondents perceived the daily use of ZYN to carry a lower relative risk (a much lower/lower chance) of developing a health condition than the daily use of only cigarettes (Section H.3.1.1.2 Report Body, Table 21 (b) (4) Table 22 (b) (4) Table 23 (b) (4) and Table 24 (b) (4)

In the Retrospective Study of Study (b) (4) the majority of ZYN users (b) (4) perceived a lower relative risk (a much lower/lower chance) of daily use of only ZYN compared with daily use of only cigarettes across the four health conditions (Section H.3.1.1.1 Report Body, Table 9).

7.7.2.2 Perceptions of the Relative Health Risk of ZYN Compared to Other TNP

In Study (b) (4), across all seven cohorts (never, former, and current TNP users), the daily use of ZYN was perceived to carry the same (b) (4) or lower (b) (4) risk relative to the daily use of only moist snuff, chewing tobacco, and snus (Section H.3.1.1.2 Report Body, Table 21 (b) (4) Table 22 (b) (4) Table 23 (b) (4) and Table 24 (b) (4)

In the Retrospective Study, the majority of ZYN users perceived a lower relative risk (a much lower/lower chance) of daily use of only ZYN compared with the daily use only of e-cigarettes (b) (4) moist snuff ((b) (4), chewing tobacco (b) (4) and snus (b) (4) across the four health conditions (Section H.3.1.1.1 Report Body, Table 9).

7.7.2.3 Perceptions of Relative Health Risk of Adding ZYN Compared to Existing TNP Usage (Dual Use)

In Study (b) (4) across all seven cohorts (never, former, and current TNP users), approximately (b) (4) of respondents perceived the daily use of ZYN to carry a lower relative risk (a much lower/lower chance) of developing a health condition than the daily use of both cigarettes and ZYN (Section H.3.1.1.2 Report Body, Table 21 (b) (4) Table 22 (b) (4) Table 23 (b) (4) and Table 24 (b) (4)

In the Retrospective Study, the majority of ZYN users (b) (4) perceived a lower relative risk (a much lower/lower chance) of daily use of only ZYN compared with dual use of cigarettes and ZYN across the four health conditions (Section H.3.1.1.1 Report Body, Table 9). Perceptions of relative risk of adding ZYN to existing TNP usage for the four health

conditions was also assessed among ZYN users (b) (4) . Results are provided in Section H.3.1.1.1 Report Body, Table 10. Findings were as follows:

- In general, ZYN was perceived to pose little additional risk to existing TNP use.
- Specifically, most ZYN users (b) (4) perceived the same relative risk of the four health conditions when adding ZYN to existing TNP use as when not adding ZYN.
- Approximately (b) (4) of ZYN users perceived a higher risk when adding ZYN to existing TNP; results varied depending on the specific TNP (eg, lowest when adding ZYN to smoking cessation aids and highest when adding to cigarette use), indicating that respondents perceived adding ZYN as posing the highest risk in the context of using the highest-risk TNP.

7.7.2.4 Perceptions of Relative Health Risk of ZYN Compared to Stop Smoking Aids

In the Retrospective Study, the majority of ZYN users (b) (4) perceived the same risk of daily use of only ZYN compared with the use of stop smoking aids across the four health conditions (Section H.3.1.1.1 Report Body, Table 9).

7.7.2.5 Perceptions of Relative Health Risk of Quitting All TNP Except ZYN Compared to Quitting All TNP

In Study (b) (4) , the majority in each cohort perceived that the daily use of ZYN carried a higher or much higher risk relative to quitting all tobacco and TNP and using nothing (Section H.3.1.1.2 Report Body, Table 21 (b) (4) Table 22 (b) (4) Table 23 (b) (4) and Table 24 (b) (4) Across all seven cohorts (never, former, and current TNP users), approximately (b) (4) perceived that the daily use of ZYN would carry the same risk relative to quitting all tobacco and TNP and using nothing.

In the Retrospective Study of Study (b) (4) , perceptions of the relative risk of quitting all TNP except ZYN versus quitting all TNP for the four health conditions was assessed among ZYN users (b) (4) Across the four health conditions, the majority of the respondents perceived continued ZYN usage (having quit all other TNP) as equally risky or of higher risk versus quitting TNP altogether (Table 28).

Table 28 Perceptions of the Relative Health Risk of Quitting All TNP Except ZYN Compared with Quitting All TNP (ZYN Users, (b) (4) (Secondary Objective 4: Study (b) (4) – Retrospective)

Relative Risk Attributed to Quitting All TNP but ZYN Compared With Quitting All TNP	Health Condition (b) (4)
A much lower chance (%)	
A lower chance (%)	
The same chance (%)	
A higher chance (%)	
A much higher chance (%)	
Don't know (%)	
Decline to answer (%)	

Source: Section H.3.1.1.1 Report Bod
CI=confidence interval; n=number of resondents; NA=not applicable; TNP=tobacco/nicotine product.

7.7.2.6 Perceptions of Relative Health Risk of Using ZYN Compared to Never Use of TNP

In Study (b) (4), the majority in each cohort perceived that the daily use of ZYN carried a higher or much higher risk relative to never having used any TNP (Section H.3.1.1.2 Report Body, Table 21 (b) (4) Table 22 (b) (4) Table 23 (b) (4) and Table 24 (b) (4) Across all seven cohorts (never, former, and current TNP users), approximately (b) (4) perceived that the daily use of ZYN would carry the same risk relative to never having used TNP.

In the Retrospective Study of Study (b) (4), the majority of ZYN users (b) (4) perceived a higher risk (a higher chance/much higher chance) of daily use of ZYN only compared with never having used any TNP across the four health conditions (Section H.3.1.1.1 Report Body, Table 9).

7.8 Misuse Potential

ZYN is intended to be placed between the gum and the upper lip and enjoyed for up to 60 minutes, then discarded, as the product is not intended to be swallowed or reused. If swallowed, the nicotine and other food-grade (or higher) ingredients found in ZYN are not harmful to adults. According to the Center for Disease Control, an average adult needs to

consume at least 50 to 60 mg of nicotine to develop overdose symptoms. Based on a study of case reports of nicotine intoxication by e-cigarette liquids, the lethal dose is assumed to be 4.4 to 8.9-fold higher (Maessen et al 2020). According to this estimate, an individual would have to ingest about (b) (4) ZYN 6 mg pouches to achieve a lethal dose. However, in reality, such exposure would result in nausea and vomiting well before the entire dose is absorbed. This circumstance may help to explain why no lethal snus intoxication has ever been reported to the Swedish Poisons Information Center despite the widespread use of snus in Sweden over more than a century with about one million current users.

8 SECONDARY AND TERTIARY EXPOSURE

ZYN is a tobacco-free, smoke-free, and spit-free nicotine pouch. ZYN does not emit any odor into the atmosphere like smoke from combustible cigarettes or vapor from e-cigarettes. Therefore, there is no secondary or tertiary harm to non-users while ZYN is consumed. In addition, the nicotine and other food-grade (or higher) ingredients found in ZYN are not harmful to adults if consumed in small quantities (eg, accidental swallowing).

9 SUMMARY AND CONCLUSIONS

To support this PMTA for ZYN, Swedish Match has sponsored four clinical studies on nicotine pharmacology and two consumer research studies, one of which included a 10-week, prospective actual use monitoring. Swedish Match has also conducted extensive chemical and toxicological analyses supplemented by quantitative risk assessment when appropriate. The conclusions from these studies are supported and extended by data from a formal, systematic literature review targeted on Swedish snus, a highly relevant bridging product for which the FDA recently issued modified risk orders. There is no published literature on the long term health effects on ZYN, because the product is relatively new with a hitherto limited market penetration in all geographies.

In summary, findings from the mentioned research program support that use of ZYN is likely associated with substantially lower health risks among individual consumers than most, or even all, of the tobacco products that currently dominate the US tobacco market (cigarettes and moist snuff). These conclusions are mainly based on the substantially more favorable toxicological profile of ZYN and the method of use which does not involve inhalation of smoke or vapor.

It is also reasonable to assume that the health risks with ZYN are lower even when compared to Swedish Match's Swedish snus products which continue to be the only products that the FDA has deemed fulfill the criteria for modified risk status. These criteria include that the product should be less risky in terms of health outcomes for individual consumers as compared to use of a conventional tobacco product, for instance, cigarettes. The criteria also stipulate that marketing of the product should benefit the population as a whole including both current users of tobacco and those who do not use such products. The basis for FDA's decision was cited to be the available data from numerous, long-term epidemiological studies on health effects of snus compared to smoking, the favorable toxicological profile of snus with substantially lower levels of HPHCs compared to other smokeless tobacco products, the existence of an established product standard, and consumer studies on the impact of the Company's proposed modified risk messaging.

In terms of toxicological profile (and hence likely impact on health effects among individual users), ZYN represents another step forward as compared to the Company's snus products; potentially carcinogenic nitrosamines (NNN and NNK), as well as the major potentially carcinogenic PAH (B[a]P), are undetectable in ZYN.

Use of ZYN does not entail heating of the product or inhalation of smoke or vapor. Therefore, effects related to formation of new compounds during product use, or effects specifically related to respiratory tract exposures, are not a concern with ZYN.

There is no HPHC exposure that is qualitatively specific to ZYN as compared to other smokeless tobacco products. Hence, it is unlikely that there is any specific health outcome with ZYN that is not already well-established for currently marketed, conventional smokeless tobacco products.

As with Swedish Match's snus products, there are no data to suggest that the marketing of ZYN has adverse effects on public health. On the contrary, the consumer research suggests that the marketing of ZYN has potential for a positive impact on public health; ZYN appeared to be an attractive alternative for some current cigarette smokers and users of conventional smokeless tobacco products. If such users were to switch to ZYN, their exposure to HPHCs associated with disease risk could be substantially reduced. The consumer research also illustrated that unintended consequences are probably minimal or non existent; current non-users of tobacco products were found to be uninterested in ZYN, and motivation to quit among current users was unaffected.

ZYN is currently marketed solely with product descriptors, ie, without any modified risk claims of reduced exposures or reduced disease risks. In the consumer research studies, this appeared to result in a reasonble understanding among the research subjects of the health risks associated with use of ZYN versus other tobacco products or non-use. Use of ZYN was perceived to be less risky than smoking, but never-use or non-use of any tobacco product was consistently scored to be associated with the least risk.

The nicotine pharmacology studies illustrated that the nicotine exposure with ZYN products with a nicotine content in the range of (b) (4) mg per pouch was comparable to or lower than that associated with use of smokeless tobacco products that are currently marketed in the US, such as moist snuff and Swedish Match's Swedish snus products. There were no data to suggest that the addictive potential of ZYN related to its nicotine delivery profile was higher than with conventional smokeless products.

Health Effects

Carcinogenic substances including NNN, NNK, and B(a)P are not quantifiable in ZYN. Since ZYN exposes the user to similar levels of nicotine to those found in snus but generally has reduced or non-measurable levels of unwanted HPHCs, health effects of snus, which contains very low levels of NNN, NNK, and B(a)P, were considered to be a measure of maximum health risks. Since there is no literature on the effects of ZYN and its adverse health effects, a systematic review of the literature on the health effects of Swedish snus, a relevant comparator product, was conducted, and limited/suggestive evidence of no association was found between snus and cardiovascular (IHD, MI, heart failure, CVD, atrial fibrillation, and stroke), cancer (head and neck, pancreatic, stomach, and lung), metabolic, or GI effects. From the literature reviewed for this PMTA, the current evidence suggests an approximately 30% decreased risk of all-cause mortality in snus users compared to smokers. There is also no evidence that snus causes

chronic obstructive lung disease, a major contributor to smoking mortality in the US (CDC 2018, CDC 2008). Use of snus or ZYN are not associated with secondary exposure and therefore decreases risk for both users and non-users. Some studies provided evidence for an increased risk in dual users (ie, snus and cigarettes) and switchers (ie, switched from cigarette use to snus use) compared to never tobacco users; however, most studies also provided evidence of decreased or statistically non-significant risks in dual users and switchers compared to smokers.

Pharmacokinetics of Nicotine

Three clinical pharmacology studies were conducted for this PMTA. In two of the studies (SM 17-01, SM 17-03), the reference product was General Snus (referred to as General PSWL 8 mg), a Swedish-style snus within the same category, which has received PMTA marketing authorizations and MRTP orders from FDA. In Study SM 18-01, the reference products included other US marketed products with higher nicotine content. Post hoc analyses were also performed across these studies.

The studies showed the following:

- There were no differences in t_{max} (approximately 1 hour) across products.
- A dose-related response in nicotine uptake (AUC and C_{max}) was observed (ZYN 3 mg < General PSWL 8 mg < ZYN 6 mg < Longhorn and ZYN 8 mg < General PSWL 2 × 8 mg).
- Data showed that the Wintergreen flavor in ZYN does not increase the delivery of nicotine, and ZYN Wintergreen delivers nicotine in the similar range to that of other Wintergreen-flavored smokeless products on the market.
- There was no evidence that the extraction of nicotine was affected by the other ZYN flavors tested (Peppermint and Spearmint).

Pharmacodyamics

Pulse rate was also collected in two of the clinical studies (Studies SM 17-01 and SM 17-03). There were no statistically significant differences in change in pulse rate at the majority of time points between the ZYN products and the reference product (General PSWL) in either study. In both studies, the larger nicotine exposure observed with ZYN 6 mg was not associated with a statistically significantly larger increase in pulse rate in the ZYN 6 mg group compared to the General PSWL group. Additionally, in Study SM 17-01, no significant difference was observed in pulse rate with respect to ZYN flavors or manufacturing production technique.

Safety

The safety and tolerability of ZYN was assessed as treatment-emergent AEs in all four clinical studies as well as in the consumer research Study (b) (4) (Patterns of Use). There were no deaths, other SAEs, or discontinuations due to AEs in any of the studies. All AEs were mild or moderate.

Oral safety as measured by dental plaque acidogenicity, changes in oral microflora, changes in plaque amount, and the appearance and number of oral mucosal lesions was also assessed in Study SM 17-02. Single-dose and 6-week *ad libitum* exposure to ZYN did not elicit an acidogenic response. During the study, substitution of snus use with ZYN improved oral mucosal lesions (also commonly referred to as snuff dipper's lesions) in healthy snus users after ZYN

administration *ad libitum* for 6 weeks (ie, the number of subjects with no lesions increased, and the number of subjects with lesions decreased during the study). There were no statistically significant changes for the subjects for the majority of plaque amount assessments or change from baseline for Lactobacilli. There was also no indication of changes in the incidence of gingival retraction during the study.

Consumer Use (Patterns and Likelihood of Use)

Swedish Match conducted two consumer research studies: a Likelihood of Use study (b) (4) which oversample people who use TNP of legal age to 24 years of age; and a Patterns of Use study (b) (4) which enrolled ZYN users and non-users. Results of the studies were subject to recall bias and self-reporting intentions, which are limited in terms of predicting behavior and can overestimate the likelihood of purchase, particularly when participants' responses have no consequences. However, Swedish Match believes these studies were robustly designed and conducted based on FDA guidances and feedback, the use of qualitative cognitive interviews prior to the execution of the quantitative surveys, the use of validated scales, and enrollment of large sample sizes that included various TNP user groups and ages.

In the Likelihood of Use study, respondents who did not use TNPs (ie, never and former users) were not likely to initiate or reinitiate TNPs after exposure to ZYN stimuli. Current TNP users demonstrated some interest in purchasing ZYN in the future. Notably, cigarette smokers with intention to quit showed greater interest in purchasing ZYN than cigarette smokers without intention to quit.

Since ZYN has been marketed in the US since 2014, Swedish Match was able to recruit actual US consumers for the Patterns of Use study to confirm that ZYN users are primarily former tobacco users. In this study, ZYN users reported an average use of (b) (4) and low rates of dual use with other TNP products. Also, ZYN users who were smokers had greater intention to quit smoking than ZYN non-users.

Perceptions of Health Risk

When evaluating the perception of absolute and relative risk of TNP types, respondents in both consumer research studies conveyed an understanding of a continuum of risk when considering use of TNP, ZYN, and cigarettes. Across all health conditions (adult tooth loss, mouth cancer, gum disease, and serious health problems), most respondents perceived low/minimal absolute risks for never having used any TNPs, low-to-moderate absolute risks for using only ZYN, and moderate-to-very high absolute risks for smoking cigarettes.

In the Likelihood of Use study, which did not enroll current ZYN users, TNP users tended to perceive lower risks of developing a health condition due to daily use of ZYN relative to other TNPs compared with TNP non-users after exposure to ZYN stimuli. Respondents consistently attributed high relative risk to the presence of cigarette usage. However, the majority of respondents across all cohorts perceived the daily use of only ZYN to carry the same or lower relative risk of each health condition as cigarettes, both cigarettes/ZYN, moist snuff, chewing tobacco, and snus. Additionally, ZYN was perceived to carry a higher relative risk compared with quitting all TNP and never using TNP.

In the Patterns of Use study, ZYN users perceived a lower relative risk of daily use of only ZYN compared with cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, and dual use of ZYN

and cigarettes. When comparing the relative risk of daily ZYN use to aids to help stop smoking or never having used any TNP, ZYN users perceived ZYN as being equally risky or of higher risk, respectively. ZYN users perceived the relative risk of adding ZYN to existing TNP use as being the same (approximately 50%) or higher (approximately 20% to 35%) ; results varied depending on the specific TNP (eg, lowest when adding ZYN to aids to help stop smoking and highest when adding to cigarette use), indicating that respondents perceived adding ZYN as posing the highest risk in the context of using the highest-risk TNP. When comparing the relative risk of quitting all TNP except ZYN versus quitting all TNP, ZYN users perceived continued ZYN usage (having quit all other TNP) as equally risky or of higher risk versus quitting TNP altogether.

Conclusions

Given the totality of evidence, Swedish Match believes that these results support that the continued marketing of ZYN would be appropriate for the protection of the public health. It is expected that there is a low likelihood of non-user uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

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APPENDIX 1 ORAL-RELATED ADVERSE EVENTS REPORTED WITH ZYN USE BY CLINICAL STUDY

MedDRA PT	Single-dose, Cross-over PK Studies			Oral Safety (Multiple Dose)
	Study 17-01 (N=20)	Study 17-03 (N=18)	Study 18-01 (N=36)	Study 17-02 (N=59)
Dry mouth	1 subject – ZYN Smooth 3 mg – 60 min (AMP); 1 subject – ZYN Smooth 3 mg – 60 min; 1 subject – ZYN Smooth 6 mg – 15 min (AMP); 1 subject – ZYN Smooth 6 mg – 15 min; 1 subject – ZYN Smooth 6 mg – 60 min	1 subject – ZYN Smooth 3 mg (AMP)	—	1 subject
Gingival pain	1 subject - ZYN Smooth 3 mg – 60 min	—	—	—
Salivary hypersecretion	2 subjects – ZYN Peppermint 3 mg; 1 subject – ZYN Smooth 3 mg – 60 min (AMP); 1 subject – ZYN Smooth 3 mg – 60 min; 1 subject – ZYN Smooth 6 mg – 60 min (AMP); 3 subjects – ZYN Smooth 6 mg – 60 min 2 subjects – ZYN Spearmint 3 mg – 60 min; 4 subjects – ZYN Wintergreen 3 mg – 60 min	—	—	—
Throat irritation	1 subject – ZYN Smooth 6 mg – 60 min; 1 subject – ZYN Wintergreen 3 mg – 60 min	—	—	—
Tongue discomfort	1 subject – ZYN Peppermint 3 mg; 1 subject – ZYN Smooth 3 mg – 60 min (AMP); 1 subject – ZYN Spearmint 3 mg – 60 min; 1 subject – ZYN Wintergreen 3 mg – 60 min	—	—	—

MedDRA PT	Single-dose, Cross-over PK Studies			Oral Safety (Multiple Dose)
	Study 17-01 (N=20)	Study 17-03 (N=18)	Study 18-01 (N=36)	Study 17-02 (N=59)
Oropharyngeal pain	—	1 subject – ZYN Smooth 3 mg (AMP)	—	—
Oral discomfort	—	—	1 subject – ZYN Smooth 8 mg	—
Gingival blister	—	—	—	1 subject
Lip pain	—	—	—	1 subject

Source: Section H.3.1.2.1 Report Body, Table 12.2-2; Section H.3.1.3.1 Report Body, Tables 14.4-2; Section H.3.1.2.2 Report Body, Table 12.2-2; and Section H.3.1.2.3 Report Body, Table 12.2-1

AE=adverse event; AMP=alternative manufacturing process; min=minutes; MedDRA=Medical Dictionary for Regulatory Activities; N=total number of subjects; PK=pharmacokinetics; PT=preferred term.