



ZYN Patterns of Use Study

Study Report

(b) (4)

Product Name:	ZYN®
First Subject Enrolled:	November 27, 2017
Last Subject Completed:	April 12, 2018
Principal Investigators:	(b) (4), (b) (6)
Sponsor:	Swedish Match North America (b) (4), (b) (6)
Sponsor Signatory:	(b) (6)
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2. SYNOPSIS

Sponsor: Swedish Match North America (SMNA) Two James Center 1021 East Cary Street, Suite 1600 Richmond, VA 23219
Name of Finished Product: ZYN [®]
Name of Active Ingredient: Not applicable
Study Title: ZYN Patterns of Use Study
Investigators: (b) (4), (b) (6) (b) (4), (b) (6)
Publication (reference): Not applicable
Studied Period: Start of data collection: Retrospective and Prospective - 27 November 2017 End of data collection: Retrospective - 16 February 2018 Prospective - 12 April 2018
Objective: The overarching research questions within this project can be stated as follows: (i) <i>How do ZYN users and ZYN non-users use Tobacco/Nicotine Products (TNP), and (ii) how do they perceive health risks associated with TNP?</i> These questions were studied with a retrospective assessment of TNP use among both ZYN users and ZYN non-users (the Retrospective Study); all study participants were of legal age to use TNP in their residential geography. Included as part of this project was a 10-week prospective study among ZYN users and ZYN non-users (the Prospective Study); Swedish Match North America (SMNA) included

objectives and related findings from the Prospective Study as part of the secondary objectives, since SMNA could not guarantee a specific sample size or composition from that study. No formal hypotheses were specified for the ZYN Patterns of Use Study.

Primary Objectives:

Data utilized from the Retrospective Study:

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

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.

2. 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.

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 were whether usage of ZYN offset usage of products such as cigarettes and smokeless tobacco.

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

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:

Data utilized from the Retrospective Study:

1. Assessment of perceptions of absolute risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) 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. Discussion sections highlight any observed divergence between ZYN users with ZYN non-users.

2. Assessment of ZYN users' perceptions of the relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) 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 (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) 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 (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) 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.

Data utilized from the Prospective Study:

5. 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.
6. 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.

Methodology: ZYN user groups were recruited directly from purchasers of ZYN through invitation stickers placed directly on ZYN canisters. A third-party vendor was hired to place the study invitation stickers on product packaging (e.g., each individual ZYN canister) for all varieties of ZYN available at retail, from November 27 – December 15, 2017. The sticker initiative targeted approximately 4,500 retail stores carrying ZYN across the 11 states where ZYN was sold at the time of recruitment.

ZYN non-users were recruited primarily through online consumer survey panels, including Lightspeed Research Panel, Survey Sampling International, and Research Now. Shortfalls in the demographic quotas of the ZYN non-users were supplemented by engaging a call center, Directions in Research, for telephone recruiting. When enrollment in the survey for the ZYN user cohort reached 40%, the (b) (4) fielding team analyzed the demographic

characteristics of the data (e.g., age, gender, racial or ethnic background, and education). The demographic characteristics of ZYN users were then used to stratify the sample of the ZYN non-users. By recruiting ZYN non-users based on demographic criteria corresponding to enrolled ZYN users, the sample recruitment plan was designed to provide matching populations regarding socio-demographic characteristics.

The retrospective portion of the research was conducted via web-based surveys. Data collected included self-reported tobacco/nicotine patterns of use over the last 30 days, reasons for ZYN use (among users), assessment of health risks from ZYN and other TNP, and additional information relevant to the study.

The prospective portion of the research utilized a subset of the participants from the retrospective portion who agreed to a web-based diary study for self-reporting daily usage of TNP over a 10-week period. The prospective study included both ZYN users and non-users.

The study 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.

Cognitive interviews were conducted prior to launching the web-based surveys to determine any potential problems with how participants understood, interpreted, and answered each survey question, including questions or response options that may have been confusing or were misinterpreted.

Number of Patients (Planned and Analyzed):

Planned: The retrospective study aimed to engage (b) (4) participants, split evenly across ZYN users and ZYN non-users. The number of respondents completing the prospective study was unknown at the outset, given its dependence on the number of entrants and compliance.

Analyzed: The retrospective study contained (b) (4) participants: (b) (4) ZYN users and (b) (4) ZYN non-users. No outliers were identified in the retrospective study. The number of respondents that completed the prospective study were (b) (4) and (b) (4) for the ZYN users and non-users, respectively. Sensitivity analysis excluded (b) (4) ZYN users and (b) (4) ZYN non-users who were identified as possible outliers within the prospective study.

Inclusion Criteria:

In addition to the already mentioned cohort definitions, respondents met all of the following criteria to be included in the study:

- At least the minimum legal age for TNP use per local state requirements.
- Were able to read and speak English.

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- At the time of the survey, were residents of one of the 11 U.S. states where ZYN is available in retail outlets (AZ, CA, CO, ID, MT, NM, NV, OR, UT, WA, WY).
 - Individuals had to provide electronic informed consent.

Exclusion Criteria:

Respondents who met any of the following criteria were excluded from the study:

- Responded as “don’t know” or “decline to answer” to specific demographics (U.S. residency, state of residence, age, gender, racial or ethnic background, or education).
- Were unwilling or unable to provide informed consent.
- Any individual employed in any of the following fields or professions: market research; marketing; advertising; employee of a TNP manufacturer; or physician.
- Any individuals who had taken part in a consumer research study on tobacco in the 2 weeks prior to the Retrospective Study.

Statistical Methods: All analyses performed for the ZYN Patterns of Use Study were descriptive in nature.

Descriptive statistics used to understand the distribution of socio-demographic and outcomes variables were based on the raw data (i.e., prior to any recoding or any aggregation required for the final presentation of results). Respondents with values for variables that were illogical or deemed unreliable, as determined by the underlying distribution, were considered for removal prior to performing the main analyses. Numeric variables were described using total sample size, number of missing observations (if applicable), means, standard deviations, medians, minimums, and maximums. Categorical variables were described using frequencies, percentages, and the number of missing observations (if applicable).

Unless otherwise specified in the table, descriptive statistics reported for the main analyses included the number of non-missing observations, means, standard deviations, and 95% confidence intervals (CIs), for numeric variables. For categorical variables, they included the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category.

The study team formatted and properly labelled the data sets (including all responses from respondents and the date that the survey was completed) using Statistical Package for the Social Sciences (IBM SPSS Statistics v23, 2015). SAS[®] software (Statistical Analysis System, version 9.4) so they were suitable for analysis. The data sets contained a subject ID number and did not contain any information that could be used to identify individual respondents.

Results Summary and Discussion:

Demographics and Respondent Characteristics:

Within the study, researchers aimed to recruit a ZYN non-user group that was demographically similar to the ZYN user cohort recruited via on-pack stickers. Cohorts were similar in terms of geography, education, gender, and ethnicity, with a majority of respondents being white males. The largest discrepancies were observed in age, marital status, presence of children, and income.

Primary Objective 1: Reported TNP use in the Last 30 Days

ZYN users mainly used smokeless tobacco products, while the ZYN non-user segment predominantly comprised smokers. ZYN users expressed much clearer intention to quit use of tobacco products (excluding ZYN, measured using the Motivation to Stop Smoking scale [MTSS]) compared with ZYN non-users.

Primary Objective 2: Reported TNP Use in the Last 30 Days Compared to Weeks Prior to Using ZYN.

Median usage of ZYN before taking the retrospective survey was 5-6 months. Thus, respondents were likely comparing usage from roughly 6-7 months prior versus the most recent 30 days, for the results below.

Prior to using ZYN, more than (b) (4) of ZYN users used a combination of multiple TNP with moist snuff and snus being the most common combination, followed by moist snuff and cigarettes.

Prior to using ZYN, (b) (4) of the user cohort reported smoking cigarettes ((b) (4) every day and (b) (4) some days). However, in the last 30 days of using ZYN, only (b) (4) of the user cohort reported smoking cigarettes ((b) (4) every day and (b) (4) some days). This finding suggests that over a hypothetical period of 5-6 months, usage of cigarettes dropped by (b) (4).

In addition to smoking, absolute use and frequency of use of other TNP from weeks prior to using ZYN to the last 30 days also declined. Prior to using ZYN, (b) (4) of the ZYN-user cohort reported using moist snuff ((b) (4) every day and (b) (4) some days). However, in the last 30 days of using ZYN, only (b) (4) of the user cohort reported using moist snuff ((b) (4) every day and (b) (4) some days). Prior to using ZYN, (b) (4) of the user cohort reported using chewing tobacco ((b) (4) every day and (b) (4) some days). Chewing tobacco usage also declined in the last 30 days of using ZYN, with (b) (4) reporting use ((b) (4) every day and (b) (4) some days).

Primary Objective 3: ZYN Usage Compliance over the Last 7 Days

Generally, ZYN users reported compliance with suggested directions for product use. The two items where compliance was low were (a) duration of usage and (b) placement of ZYN pouch in the mouth. First, 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 mins, per instruction, whereas (b) (4) reported that they always do. Second, (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.

Secondary Objective 1 (Retrospective): Perceptions of Absolute Risk

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, and cigarettes. Specifically, respondents perceived the absence of any TNP use as having minimal health risk, usage of ZYN as having low-to-moderate health risk (ZYN users only), and cigarette smoking as having moderate-to-very high risk.

Secondary Objective 2 (Retrospective): Perceptions of Relative Risk of ZYN to Other TNP

When evaluating relative risk of TNP types and usage scenarios, ZYN users exhibit an understanding of a continuum of risk when considering the use of ZYN compared with a variety of TNP options. Compared with cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, and dual use of ZYN and cigarettes, ZYN users perceived a lower relative risk of daily use of only ZYN. When comparing the relative risk of daily use of ZYN to aids to help stop smoking or never having used any TNP, respondents perceived ZYN as being equally risky or of higher risk, respectively.

Secondary Objective 3 (Retrospective): Perceptions of Relative Risk of Adding ZYN to Existing TNP Usage.

Findings suggest that generally, ZYN is perceived to pose little additional risk to existing TNP use. Specifically, a majority of ZYN users (just over (b) (4)) perceived the same risk of health conditions when adding ZYN to existing TNP relative to not adding ZYN. About (b) (4) of ZYN users perceived a higher risk when adding ZYN to existing TNP; results varied depending on the specific TNP (e.g., 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.

Secondary Objective 4 (Retrospective): Perceptions of Relative Risk of Quitting All TNP Except ZYN to Quitting All TNP.

Across health conditions, when comparing the relative risk of quitting all TNP except ZYN versus quitting all TNP, respondents perceived continued ZYN usage (having quit all other TNP) as equally risky or of higher risk versus quitting TNP altogether.

Secondary Objective 5 (Prospective): Exploration of Daily TNP Patterns of Use Among ZYN Users and ZYN Non-users, Including Reasons for ZYN Use.

ZYN users reported smoking substantially fewer cigarettes than non-users. The number of respondents who reported smoking cigarettes every day or some days dropped among ZYN users throughout the study, whereas cigarette use remained consistent among ZYN non-users.

Further, the percentage of participants who smoked cigarettes every day or some days (defined as at least 1 day a week) decreased for ZYN users from week 1 ((b) (4)), to week 10 ((b) (4)). In contrast, no change was observed for ZYN non-users throughout the 10 weeks. In summary, smokers who used ZYN reported fewer days smoking at least one cigarette than non-users. These findings are consistent with ZYN users' intention to quit cigarettes, as assessed with MTSS. The majority of ZYN users reported that their reason for using ZYN was to reduce or to help quit cigarette use, which was supported by the diary data.

Similar to cigarettes, we observed a pattern of decreasing use of moist snuff. Specifically, ZYN users' use of moist snuff everyday and some days dropped from ((b) (4)) (week 1) to ((b) (4)) (week 10). The reduction in moist snuff usage among ZYN non-users was less steep; ((b) (4)) (week 1) to ((b) (4)) (week 10). Considering these results in context, many ZYN users entered the prospective study having used ZYN for a substantive length of time; median usage = 5-6 months. Arguably, their usage habits were established and consistent by the time they began day 1 of the prospective study. Evidence from the retrospective data supports that switching/quitting from other TNP had already occurred prior to starting the prospective study. Therefore, seeing evidence of continual reduction in cigarette and other TNP usage during the 10-week prospective period is noteworthy.

There was no observed difference in the daily number of pouches of ZYN used, the duration of each pouch's use, or the number of respondents reporting use of ZYN everyday throughout the 10-week period. Although there was a slight decrease in the number of reported participants who used ZYN every day or some days, the number of participants that reported using ZYN **only** increased throughout the Prospective Study. ZYN users also reported little desire to quit use of ZYN, although the percentage that did not use ZYN at all increased across the 10 weeks ((b) (4)) in week 1 to ((b) (4)) in week 10). The most common reasons for using ZYN at the end of the 10 weeks were: *to help reduce/quit cigarette smoking; to use in environments where other TNP were inappropriate/not allowed; less harmful than cigarettes; no one can tell it is being used; and ease of use.*

Secondary Objective 6 (Prospective): Comparison of the Tendencies of ZYN Users to Quit TNP or in Complete Substitution of Other TNP.

By weeks 9 and 10, ((b) (4)) of ZYN users reported completely substituting ZYN in place of other TNP and ((b) (4)) of ZYN users had quit all TNP.

Strengths and Limitations of the Study: This study was conducted based on fundamental social and statistical science, with valuable guidance by the Center for Tobacco Products (CTP Addendum, 2017), to evaluate the risks and benefits to the population, including users and non-users of the tobacco product.

The resulting study featured many strengths. The study benefitted from the substantial number of ZYN users recruited through the on-pack invitations, a number higher than the original target. Continuation of participants in the Prospective Study exceeded expectations, and compliance was high once entered. Additionally, the use of qualitative cognitive interviews prior to the execution of the quantitative survey strengthened the design of the web-based survey. Cognitive interviews ensured that the materials were appropriate and sufficiently clear to respondents. The study results were robust enough to withstand the inclusion of outliers. As the pattern of results were the same in the full sample analysis and the sensitivity analysis (conducted for prospective study), it appeared that the inclusion of outliers did not have a substantive impact on the findings.

Finally, in virtually all cases, survey questions utilized validated scales, or scales directly comparable to studies in literature. In particular, usage of the MTSS allowed for simple, justifiable interpretation. Scales used in risk perception questions line up with other tobacco-related research, such as HINTS.

There were several limitations to the current study, none of which should draw concern regarding data integrity. Although we attempted to match the ZYN non-user cohort to the ZYN user cohort, smoking incidence (30 days before using ZYN for ZYN users) differed across these cohorts and was higher among non-users. ZYN users in our study were likely to be relatively established in their use of ZYN, and therefore, we might be underestimating baseline cigarette use that would have been seen among those who just began using ZYN. Both the retrospective and prospective data from this study were dependent on respondent self-reporting, and subsequently reported variables may be subject to recall bias or attempts at appeasement of the investigators. Self-reported data collection is a standard approach, and any potential problems with recall bias were anticipated to be constant across time points. Also, the inclusion of a robust sample size helps alleviate some of these concerns.

Researchers could not analyze respondents who responded, “don’t know” or “decline to answer”. As in prospective clinical studies, we set evaluability rules; as such, those who responded “don’t know” or “decline to answer” were excluded from the evaluable subset of responders, which was the primary population for analyses.

While driven by best practice and highest likelihood of obtaining enough of the right respondents, recruitment methods for ZYN users and non-users were not consistent. ZYN users were recruited from stickers placed on ZYN cannisters. The ZYN non-users were recruited utilizing online consumer survey panels with supplements from a call center, with recruitment criteria based on the demographics represented in the ZYN user cohort. Even with efforts to ensure a representative sample using stratification, the precise proportion of subgroups in the study sample could not be completely controlled. In fact, regardless of how respondents were recruited, the possibility exists that the people who declined the opportunity to participate in the research may differ in a systematic way from the people who accepted the opportunity.

Conclusion: The Patterns of Use study was a two-part observational study intended to assess the differences in usage of TNP between ZYN users and non-users, intention to quit TNP, compliance, and perceptions of risk. The first part of the study, “Retrospective”, evaluated past usage of TNP (before and after ZYN), compared TNP use between ZYN users and non-users,

assessed intention to quit TNP, and evaluated perceptions of risk. The second part of the study, “Prospective”, monitored the continued use of TNP and intention to quit TNP in a 10-week period among a subgroup of the Retrospective study respondents.

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 that:

- 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 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.

Final Date: 06-August-2018

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition
AE	Adverse Event
CA	California
CAPTCHA	Completely Automated Public Turing Test to Tell Computers & Humans Apart
CO	Colorado
CTP	Center for Tobacco Products
DIR	Directions in Research
FDA	FDA Food and Drug Administration
FTP	File Transfer Protocol
HCP	Health Care Professional
ICF	Informed Consent Form
ID	Idaho
IP	Internet Protocol
IRB	IRB Institutional Review Board
MRTP	Modified Risk Tobacco Product
MSG	Marketing Systems Group
MT	Montana
MTSS	Motivation to Stop Scale
NCHS	National Center for Health Statistics
NE	Nevada

Abbreviation or Specialist Term	Definition
NM	New Mexico
OMB	Office of Management and Budget
OR	Oregon
PATH	Population Assessment of Tobacco and Health
PII	Personally Identifiable Information
PMTA	Premarket Tobacco Product Application
RDD	Random Digit Dialing
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMNA	Swedish Match North America, Inc.
SSI	Survey Sampling International
TNP	Tobacco/Nicotine Product(s)
UT	Utah
WA	Washington
WY	Wyoming
ZYN non-users	ZYN non-users who use tobacco products

5. RESPONSIBLE PARTIES

5.1 Investigator and Contributors

Principal Investigators:	(b) (4), (b) (6)
(b) (4) Project Team:	(b) (4), (b) (6)

5.2 Sponsor

Sponsor:	Swedish Match North America (b) (4), (b) (6)
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6. ETHICS

6.1 Institutional Review Board (IRB)

Documented approval from a central IRB in the U.S. was obtained prior to the initiation of the study. Sterling, IRB (Atlanta, Georgia) approved this study. When necessary, an extension, amendment or renewal of the IRB approval was obtained from Sterling, IRB and forwarded to Swedish Match North America (SMNA).

6.2 Ethical Conduct of the Study

The study was carried out within an approved indication and in accordance with Center for Tobacco Products (CTP) guidance on data for human studies designed to evaluate the risks and benefits to the population as a whole (CTP Addendum, 2017). Additionally, (b) (4) conducts all our research in accordance with the requirements of our Quality System, which confirms to ISO 20252:2012 the International Standard for Market Research, Certification Number: 1019.

6.3 Respondent Information and Consent

Prior to beginning the survey, potential respondents were provided with a statement of informed consent. The consent informed potential respondents that participation in the study was voluntary, and that responses remained confidential. It also included information about the goals of the study, the approximate length of the survey, and incentives for participation. Lastly, the statement of informed consent provided potential respondents with the resource references to address any concerns they could have. A link to each panel was given if the respondent had any specific questions about the survey instrument or incentives for participation.

After potential respondents read the statement of informed consent, they were asked, “Do you voluntarily agree to participate in this study?” Respondents who selected “I agree to participate” were able to complete the survey. At any time during survey completion, the respondent could choose to exit the survey should they decided not to participate any further. Data provided by a respondent who exited the survey prematurely were not utilized in any analyses. Respondents who selected “I do not agree to participate” were thanked for their time before exiting. IRB written approval / favorable opinion of the electronic informed consent form and any other written information provided to respondents were obtained prior to the initiation of the study.

7. INTRODUCTION

7.1 Background

The Family Smoking Prevention and Tobacco Control Act, signed into law in 2009, gave the Food and Drug Administration (FDA) the power to regulate tobacco products and established the Center for Tobacco Products (CTP) within the FDA. The law gives the CTP authority to regulate the manufacturing, marketing/advertising content, and sale of tobacco/nicotine products (TNP), which include cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, cigars, cigarillos, and filtered cigars filled with tobacco, pipe tobacco, hookah and water pipe tobacco, and aids to help stop smoking. The FDA requires that the marketing of a new tobacco product be appropriate for the protection of the public health as determined “on the basis of well-controlled investigations” (FDA Guidance for Industry, 2011).

The CTP has provided draft guidance on data for human studies designed to evaluate the risks and benefits to the population, including users and non-users of the tobacco product (Center for Tobacco Products, 2011; [FDA Guidance for Industry, 2016](#)). Essentially, CTP will require research-based evidence that demonstrates, in general: (1) existing tobacco product users do not increase consumption, (2) non-tobacco users do not start using, and (3) former tobacco users do not re-start use of tobacco. Products marketed in the U.S. after February 15, 2007 must obtain a marketing authorization from the FDA, through a premarket tobacco product application (PMTA) or a Substantial Equivalence (SE) report, or they can no longer be sold in the U.S.

Swedish Match North America (SMNA) began selling ZYN[®] in 2014. ZYN delivers nicotine derived from tobacco, but the ZYN product itself does not contain tobacco leaves. It comes in a small pouch that contains nicotine flavoring elements, and other ingredients required to ensure shelf stability. SMNA has no current intention of marketing ZYN as a smoking cessation product, but rather as a nicotine delivery product that requires no spitting, produces no off-putting odors, is smoke-free, and comes in a variety of flavors and nicotine strengths. Because of the Tobacco Control Act requirements, SMNA must submit a PMTA application to continue marketing the ZYN product.

7.2 Rationale

The output of this research will be submitted to the FDA as part of the ZYN PMTA. For this purpose, the primary objective of the Patterns of Use Study is to evaluate TNP patterns of use among ZYN users and ZYN non-users historically, and secondarily, describe behavior over time, under real world conditions.

8. STUDY OBJECTIVES

The overarching research questions within this project can be stated as follows: *(i) How do ZYN users and ZYN non-users use Tobacco/Nicotine Products (TNP), and (ii) how do they perceive health risks associated with TNP?* These questions were studied with a retrospective assessment of TNP use among both ZYN users and ZYN non-users (the Retrospective Study); all study

participants were of legal age to use TNP in their residential geography. Included as part of this study was a 10-week prospective study among ZYN users and ZYN non-users (the Prospective Study); SMNA included objectives and related findings from the Prospective Study as part of the secondary objectives, since SMNA could not guarantee a specific sample size or composition from that study. No formal hypotheses are specified for the ZYN Patterns of Use Study.

8.1 Primary Objectives

Data utilized from the Retrospective Study:

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

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.

2. 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.

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.

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

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.

8.2 Secondary Objectives

Data utilized from the Retrospective Study:

1. Assessment of perceptions of absolute risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) 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. Discussion sections highlight any observed divergence between ZYN users with ZYN non-users.

2. Assessment of ZYN users' perceptions of the relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately)

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 (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) 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 (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) 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.

Data utilized from the Prospective Study:

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.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

9.1.1 Study Design

The ZYN Patterns of Use Study consisted of two distinct phases, meant to gain an understanding of how ZYN is and has been used among consumers. Each project included ZYN users and non-users, to allow for more informed investigation. Each study relied upon its own survey instrument; cognitive interviews informed retrospective and prospective surveys to ensure clear communication of survey items to respondents. The Retrospective Study utilized a cross-sectional design to measure recalled TNP usage among ZYN users and ZYN non-users. The Prospective Study longitudinally evaluated TNP patterns of use among ZYN users and ZYN non-users over a 10-week observation period. More information about cognitive interviews can be found in Protocol

Section 8.2 ([Attachment 17.5](#)) and in the Cognitive Interview Report ([Attachment 17.7](#)), while more information on the study survey is available in the ZYN Patterns of Use Study Questionnaire ([Attachment 17.4](#)).

With ZYN in limited distribution, incidence of ZYN users among the general population would be quite low. To recruit users of ZYN most efficiently, an invitation sticker was placed directly on ZYN canisters. A third-party vendor was hired to place these study invitation stickers on product packaging (e.g., each individual ZYN canister) for all varieties of ZYN available at retail, from November 27 – December 15, 2017. The sticker initiative targeted approximately 4,500 retail stores carrying ZYN across the 11 states where ZYN is sold. More information on recruitment of ZYN users through the ZYN invitation sticker initiative is available in the ZYN Patterns of Use Study Protocol ([Attachment 17.5](#)).

ZYN non-users were recruited through online consumer survey panels, including (b) (4), (b) (4), and (b) (4). Shortfalls in the demographic quotas of the ZYN non-users were supplemented by engaging a call center, (b) (4), for telephone recruiting. When enrollment in the survey for the ZYN user cohort reached (b) (4), the (b) (4) fielding team analyzed the demographic characteristics of the data (e.g., age, gender, racial or ethnic background, and education). The demographic characteristics of ZYN users were then used to stratify the sample of the ZYN non-users. By recruiting ZYN non-users based on demographic criteria corresponding to enrolled ZYN users, the sample recruitment plan was designed to provide matching populations regarding socio-demographic characteristics. Participants in the ZYN Patterns of Use Study were only those who meet inclusion and exclusion criteria (explained in [Section 9.2.1](#) and [Section 9.2.2](#)). For more information on recruitment of ZYN non-users refer to the ZYN Patterns of Use Study Protocol ([Attachment 17.5](#)).

After recruitment, ZYN users and ZYN non-users accessed a 10 to 20-minute Retrospective survey where participants were asked to self-report current TNP use. Upon completion of the Retrospective survey, respondents were invited to participate in the Prospective Study. The Prospective Study survey instrument administered to ZYN users and ZYN non-users who accepted the invitation to the Prospective Study 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. Additionally, individuals participating in the Prospective Study could miss up to two daily surveys in each week of the 10-week observational period. Failure to complete the minimum five daily surveys per week resulted in that participant being removed from the study.

9.2 Study Cohorts

The study sample consisted of the adult population of US states where ZYN is available in retail outlets (AZ, CA, CO, ID, MT, NM, NV, OR, UT, WA, WY), and who are of legal age for TNP use. To meet the objectives of the ZYN Patterns of Use Study, the study included respondents from the following cohorts described in [Table 1](#). ZYN users and ZYN non-users were defined by self-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. 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. In the PATH study, a threshold of lifetime use is established

for cigarette use, which is having smoked 100+ cigarettes in a lifetime and for all other TNP is based on recollection of ever using the TNP fairly regularly. Current use was based on now using the product every day or some days (U.S. Department of Health and Human Services, PATH, 2017).

Table 1: Patterns of Use Study Cohorts

Current ZYN users	<p>All ZYN users were recruited through the canister sticker program. Users were then confirmed through the screener to:</p> <ul style="list-style-type: none"> • Have used nicotine pouches fairly regularly; and, • Now use ZYN pouches every day or some days.
ZYN non-users who use TNP(s)	<ul style="list-style-type: none"> • Have never used ZYN OR • Have NOT used ZYN regularly AND do NOT currently use ZYN every day or some days <p>AND <u>AT LEAST ONE</u> OF THE FOLLOWING:</p> <ul style="list-style-type: none"> • Have smoked 100 or more cigarettes during lifetime AND currently smoke cigarettes every day or some days AND/OR • For any of the following products, have been a regular user AND now uses the product every day or some days: <ul style="list-style-type: none"> ○ 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)

9.2.1 Inclusion Criteria

In addition to the cohorts to be included in this study, respondents had to meet the following criteria to be included:

- Minimum legal age for TNP use per local state requirements.
- Able to read and speak English.
- Currently a resident of one of the 11 U.S. states where ZYN was available in retail outlet (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY).
- Individuals who provide electronic informed consent.

9.2.2 Exclusion Criteria

Respondents who meet any of the following criteria were excluded from the study:

- Responded as “don’t know” or “decline to answer” to specific demographics (gender, geographical region, ethnicity, or education), used for balancing cohorts.
- Unwilling or unable to provide electronic informed consent.
- Individuals employed in any of the following fields or professions: market research, marketing, advertising, manufacturers of TNP, or physicians.
- Individuals who had taken part in a consumer research study on tobacco in the past 2 weeks prior to the Retrospective Study.

9.3 Determination of Sample Size

The ZYN Patterns of Use study was run in conjunction with a Likelihood of Use study; these studies in tandem provided the consumer research required to support the PMTA.

While the Patterns of Use study primarily asked questions meant to report behaviors, as opposed to providing opinions, the decision was made to mirror the Likelihood of Use sampling algorithm. Hence, the Patterns of Use study precision analysis was performed under the following assumptions: a confidence interval of 95% ($\alpha=0.05$), a standard deviation of 3.74, a small interval half-width, and a probability of achieving the desired precision of 0.99.

The precision analysis suggested a sample size of (b) (4) in the Retrospective Study would be appropriate (Note that the Likelihood of Use study mentioned, suggested a sample size of (b) (4) of interest). In total, the planned study sample for the Retrospective Study was (b) (4), with (b) (4) respondents in each cohort. Table 2 presents the expected sample size for each cohort compared to the actual sample size, while also noting that sample sizes for the Prospective Study were an undetermined subset of those completing the Retrospective Study and consisted of only participants who completed all 10 weeks of the prospective observational period.

Table 2: Sample Sizes for the Retrospective and Prospective Studies.

(b) (4)



9.4 Variables of Relevance to the Study

9.4.1 Outcomes

9.4.1.1 Outcomes for Primary Objectives

Outcomes that were used to evaluate the primary objectives are as follows:

Reported use in the last 30 days was assessed by using one item and observing frequency of use for each TNP currently used over the last 30 days. The item was based on the approach employed in PATH for observing current TNP use ([U.S. Department of Health and Human Services, PATH, 2017](#)). Response options for frequency of use included “Every day,” “Some days,” “Not at all,” “Don’t know” and “Decline to answer.”

Intention to quit respective TNP was assessed using one item for each TNP and assessing intention to quit the respective TNP. Intention to quit TNP was measured using the Motivation to Stop Scale (MTSS [[Kotz et al., 2013](#)]). The MTSS consists of one item with seven response options ranging from 1 (lowest) to 7 (highest level of motivation to stop smoking), also including “Don’t know.” Scale developers found that odds of quit attempts increased linearly with increasing levels of motivation. In the current study, we used the MTSS both for assessing intention to quit cigarettes and for other TNP. Consistent with published research using the MTSS, we reported the mean MTSS score ([Hummel et al., 2017](#)). The MTSS was selected for use in the ZYN Patterns of Use Study due to its brevity and validation as a strong and accurate predictor of quit attempts (Kotz et al., 2013).

Reported use in the weeks prior to initiating ZYN usage was assessed by using one item and observing frequency of use for each TNP used by a respondent. The item is based on the approach employed in PATH for observing current TNP use ([U.S. Department of Health and Human Services, PATH, 2017](#)). Response options for frequency of use included “Every day,” “Some days,” “Not at all,” “Don’t know” and “Decline to answer.”

Level of compliance with ZYN usage instructions was assessed using one custom item for each of four examples representing proper and improper ZYN use. Items corresponding to proper use included “Placed a ZYN pouch between my gum and upper lip” and “Used one ZYN pouch at a time.” Items corresponding to improper use of ZYN included “Used one ZYN pouch for more than 60 minutes” and “Cut the ZYN pouch open and used the pouch contents.” Response options for each item included “Always,” “Sometimes,” “Never,” “Don’t know” and “Decline to answer.”

9.4.1.2 Outcomes for Secondary Objectives

Outcomes that were used to evaluate the secondary objectives were as follows:

Perceptions of absolute risk were assessed using a single-choice scale (5-point Likert scale, fully anchored; from 1= Very low chance to 5= Very high chance, also including “Don’t know” and “Decline to answer”) for each of four health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems). This scale was created and used by working with a validated risk perception scale from HINTS and making slight, appropriate modifications. ([National Cancer Institute, HINTS, 2005](#)).

Perceptions of relative risk were assessed using a single-choice scale (5-point Likert scale, fully anchored; from 1= A much lower chance to 5= A much higher chance, also including “Don’t know” and “Decline to answer”) for each of the four health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems), contrasting ZYN use with several other risk exposures. The risk exposures that were assessed for each health condition included use of ZYN versus the daily use of other TNP, aids to help stop smoking, and never having used any TNP; and quitting all TNP relative to quitting all TNP except for ZYN. This scale was created and used by working with a validated risk perception scale from HINTS and making slight, appropriate modifications. (National Cancer Institute, HINTS, 2005).

Average daily reported use during the prospective observational period was assessed based on one item in the daily prospective survey assessing TNP use for each TNP; namely, the number of times each TNP was used in each day of the observational period. Observations of daily TNP use were used to derive average daily use of each TNP per week in the 10-week observational period.

Weekly frequency of use during the prospective observational period was derived based on one item in the daily prospective survey assessing TNP use for each TNP; namely, the number of times each TNP was used in each day of the observational period. These observations were used to derive weekly frequency of use for each TNP. For example, respondents participating in the Prospective Study who report using a TNP every day for a given week based on non-missing daily surveys (e.g., usage for 5/5, 6/6, or 7/7 daily surveys) were considered “Every day” users.

Respondents participating in the Prospective Study who reported using a TNP at least one day, but not every day, (e.g., usage for 1/5, 1/6, 3/6, 2/7, etc., daily surveys) based on non-missing daily surveys were considered “Some days” users. Finally, respondents participating in the Prospective Study who did not report any TNP use based on non-missing daily surveys (e.g., usage for 0/5, 0/6, or 0/7 daily surveys) were considered “Not at all” users. Derived outcomes based on the prospective survey items were based on the approach employed in PATH for observing current TNP use ([U.S. Department of Health and Human Services, PATH, 2017](#)).

Weekly use of ZYN with other TNP was derived based on one item in the daily prospective survey assessing TNP use for each TNP; namely, the number of times each TNP was used in each day of the observational period. These observations were used to derive whether respondents used ZYN only, ZYN+cigarettes, ZYN+other TNP (excluding cigarettes), ZYN+smokeless TNP (e.g., moist snuff, chewing tobacco, or snus), ZYN+snus, ZYN+chewing tobacco, or ZYN+moist snuff in each week of the 10-week observational period.

Intention to quit each TNP during the prospective observational period was assessed using the MTSS, described in detail above ([Kotz et al., 2013](#)).

Reasons for ZYN use were assessed using one item in the biweekly survey assessing why respondents had used ZYN. Respondents were allowed to select more than one reason. Reasons for using ZYN included:

- To help me reduce my cigarette smoking;
- To help me quit smoking cigarettes;
- To help me reduce my use of tobacco products other than cigarettes;
- To help me quit using tobacco products other than cigarettes;
- To use in environments where other tobacco/nicotine products are not considered appropriate (e.g., church, etc.);
- To use in environments where other tobacco/nicotine products are not allowed (e.g., airplane, etc.);
- Less harmful to my health than cigarettes;
- Less harmful to my health than other tobacco products, excluding cigarettes;
- To avoid spitting as required with other products;
- To add variety to the products I use;
- Comes in flavors I like;
- Does not cause me to smell like smoke/tobacco;
- Comes in two different levels of nicotine strength;
- Less harmful for those around me than cigarettes;
- More acceptable to non-tobacco users;

-
- No one can tell when I am using it;
 - I was just curious to see what it was like;
 - Ease of use;
 - Recommended by person who works in the store where I buy my TNP;
 - None of the above.
 - Additional response options included “Don’t know” and “Decline to answer”.

Percent of days ZYN is used was derived based on one item in the daily prospective survey assessing ZYN usage. The item reported the number of ZYN pouches used each day. The average percent of days ZYN is used was calculated as the percentage of non-missing days in each week where at least one ZYN pouch was used.

Average number of ZYN pouches used per day were derived based on one item in the daily prospective survey assessing ZYN usage. The item reported the number of ZYN pouches used each day. The average number of ZYN pouches used per day was calculated as the average number of ZYN pouches used for non-missing days in each week.

Average number of minutes ZYN was kept in mouth were derived based on one item in the daily prospective survey assessing ZYN usage. The item reported the typical duration of time an individual ZYN pouch was used in the given day. The average number of minutes ZYN was kept in the mouth was calculated based on the duration of time a typical ZYN pouch was kept in the mouth for non-missing days in a given week.

Quitting all TNP use was derived based on one item in the daily prospective survey assessing usage of each TNP, based on daily TNP use during weeks 1 and 2 as well as TNP usage patterns in the last 30 days of the observational period. Respondent TNP use during weeks 1 and 2 will be used to establish TNP use at the beginning of the prospective observational period. Quitting TNP was determined based on respondents reporting zero TNP use over weeks 9 and 10.

Complete substitution of TNP use was derived based on one item in the daily prospective survey assessing usage of each TNP, based on daily TNP use during weeks 1 and 2 as well as weeks 9 and 10 of the prospective observational period. Respondent TNP use during weeks 1 and 2 will be used to establish TNP use at the beginning of the prospective observational period. Similarly, TNP use during weeks 9 and 10 was used to determine TNP use at the end of the prospective observational period. ZYN users who used other TNP during weeks 1 and 2 of the prospective observational period but only ZYN in weeks 9 and 10 were considered to have completely substituted ZYN in place of other TNP.

Summaries of the outcomes for primary and secondary objectives, including measurement domain, subcategories, measurement details, and metrics, are presented in SAP [Tables 3-11](#) (listed in [Appendix 16.1](#); [Attachment 17.6](#)).

9.4.2 Respondent Characteristics

Sociodemographic Variables

- **State of residence** which was assessed using a single item asking the respondent what state they spend most days of the year in. State of residence must be one of the eleven states in which ZYN is sold (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY).
- **Age of the respondent** was assessed using a single item asking the respondent how many years old they are. Age of respondent was categorized and reported using the following age groups: 18-20, 21-24, 25-34, 35-44, 45-54, and 55+ years old.
- **Gender** was assessed using a single item asking the respondent if they are male or female.
- **Racial or ethnic background** was assessed using a single item asking the respondent which best describes their racial/ethnic background. Response options included: Caucasian/White, Black/African American, Hispanic (e.g., Latin American, Mexican, Puerto Rican, Cuban), Asian or Pacific Islander, Native American or Alaskan native, mixed racial background, or other.
- **Highest grade or level of school completed** was assessed using a single item asking the respondent which response corresponds to the highest level of education they have attained. Response options included: Less than high school, some high school – no diploma, General Educational Development (GED), high school graduate – diploma, some college but no degree, Associate degree, Bachelor’s degree (e.g., BA, AB, BS), or Post-graduate degree (e.g., MBA, PhD, JD, etc.).
- **Marital Status** was assessed using a single item asking the respondent their marital status. Response options included: Now married, widowed, divorced, separated, never married, and decline to answer.
- **Number of adults who live in the household** was assessed using a single item asking the respondent for the number of individuals living in the household who are over 18 years old. Decline to answer is also available as a response option. Number of adults in the household was categorized for reporting as 1, 2, 3, 4, or 5+.
- **Number of children who live in the household** was assessed using a single item asking the respondent for the number of individuals living in the household who are under 18 years old. Decline to answer is also available as a response option. Number of children in the household was categorized for reporting as 1, 2, 3, 4, or 5+.
- **Household income in the last 12 months** was assessed using a single item asking respondents which category best describes their total household income in the last 12 months. Response options included: Less than \$10,000, \$10,000 to \$14,999, \$15,000 to \$24,999, \$25,000 to \$34,999, \$35,000 to \$49,999, \$50,000 to \$74,999, \$75,000 to \$99,999, \$100,000 to \$199,999, \$200,000 or more, don’t know, or decline to answer. Household income will be categorized for reporting as less than \$25,000, \$25,000-49,999, \$50,000-74,999, \$75,000-99,999, \$100,000 or more.

9.5 Time Points of Importance

Time points of importance in the Retrospective Study occur under primary objective 1, TNP patterns of use. Specific time points of importance in the Retrospective Survey include the last 30 days, the weeks prior to starting ZYN, and the last 7 days, which correspond to reported TNP use in the last 30 days, TNP use in the weeks prior to using ZYN and compliance with ZYN usage instructions over the last 7 days (both only among ZYN users). Specific time points of importance in the Prospective Study include the prior day and the previous two weeks, which correspond to daily reported TNP use in the daily survey and intention to quit TNP in the biweekly survey.

10. STATISTICAL ANALYSIS

10.1 Study Analysis

All analyses performed for the ZYN Patterns of Use Study were descriptive in nature.

Descriptive statistics used to understand the distribution of socio-demographic and outcomes variables (see [Section 9.4.1](#) and [Section 9.4.2](#)) were based on the raw data (i.e., prior to any recoding or any aggregation required for the final presentation of results). Respondents with values for variables that were illogical or deemed unreliable, as determined by the underlying distribution, were considered for removal prior to performing the main analyses (see [Section 11.2](#) and [Section 11.4](#) for details regarding this process). Numeric variables were described using total sample size, number of missing observations (if applicable), means, standard deviations, medians, minimums, and maximums. Categorical variables were described using frequencies, percentages, and the number of missing observations (if applicable).

Unless otherwise specified in the table, descriptive statistics reported for the main analyses included the number of non-missing observations, means, standard deviations, and 95% confidence intervals (CIs), for numeric variables. For categorical variables, they included the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category.

The study team formatted and properly labelled the data sets (including all responses from respondents and the date that the survey was completed) using Statistical Package for the Social Sciences ([IBM SPSS Statistics v23, 2015](#)). SAS[®] software (Statistical Analysis System, version 9.4) so they were suitable for analysis. The data sets contained a subject ID number and did not contain any information that could be used to identify individual respondents.

10.2 Socio-demographics

Descriptive statistics were reported for all socio-demographic variables outlined in [Section 9.4.2](#). Specifically, state of residence, age of respondent, gender, racial or ethnic background, highest grade or level of school completed, marital status, number of adults who live in the household, number of children who live in the household, and household income in the last 12 months, was reported for both ZYN users and ZYN non-users.

10.3 Statistical Analysis by Study Objective

10.3.1 Primary Objective

Descriptive statistics for accomplishing primary objectives were reported for patterns of TNP use (for both ZYN users and non-users) as well as compliance with ZYN usage instructions among ZYN users. Descriptive statistics included the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category for categorical variables. SAP Tables 12 to 14 (listed in [Appendix 16.1](#); Attachment 17.6) provide summaries of the analyses that were used to accomplish the primary objectives, including the objective, outcomes, cohorts, and the statistical analysis.

10.3.2 Secondary Objective

Descriptive statistics for accomplishing secondary objectives utilizing data from the Retrospective Study were reported for both perceptions of absolute risk and perceptions of relative risk. Descriptive statistics included the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category, for categorical variables. SAP Tables 15 to 18 (listed in [Appendix 16.1](#); Attachment 17.6) provide summaries of the analyses that were used to accomplish the secondary objectives for the Retrospective Study, including the objective, outcomes, cohorts, and the statistical analysis.

Descriptive statistics for accomplishing secondary objectives utilizing data from the Prospective Study were reported for daily TNP patterns of use as well as incremental use, supplemental use, quitting all TNP excluding ZYN, and quitting all TNP including ZYN. Descriptive statistics included the number of non-missing observations, means, standard deviations, and 95% CIs. SAP Tables 19 and 20 (listed in [Appendix 16.1](#); Attachment 17.6) provide summaries of the analyses that will be used to accomplish the secondary objectives that are based on data from the Prospective Study, including the objective, outcomes, cohorts, and the statistical analysis. Respondents were allowed two missing daily surveys per week, a policy utilized to allow flexibility for human inconsistency while maintaining a consistent flow of data pertaining to respondent usage.

10.4 Changes in the Conduct of the Study or Planned Analyses

There were two amendments to the protocol. The summary of changes in the conduct of the study from the procedures outlined in the original protocol are briefly listed below:

- Amendment 1 (issued on November 15, 2017): Changes based on initial CTP feedback on General Snus MRTP amendment protocol.
- Amendment 2 (issued on May 28, 2018): Changes based on new information and additional background obtained from January 24-25, 2018 Tobacco Products Scientific Advisory Committee Meeting and public availability of Camel Snus/RJ Reynolds Tobacco Company MRTP application.

In addition to the amendments to the protocol listed above, there were necessary changes during the fielding of the study. The ZYN user cohort was drawn from SMNA's sticker campaign, in the 11 states where ZYN was sold, while the ZYN non-user cohort was drawn from panel (and phone if needed). Original panels and phone sample did not provide enough potential respondents to reach the desired quota targets for the ZYN non-user cohort. An additional panel (MFour) was brought in to assist in trying to reach the the desired demographics for the ZYN non-user cohort. Researchers aimed to proportionally match the ZYN non-user cohort with the states and demographic profile of the ZYN user cohort, however achieving sufficient sample required relaxing the quota by state. In the end, the achieved demographic quotas for ZYN non-users were within $\pm 20\%$ of the ZYN user demographics.

There was one amendment made to the SAP issued on June 6, 2018. These changes did not pertain to the planned analyses in the SAP. A summary of the changes to the original SAP are briefly listed below:

- Format edits to the table shells and accompanying footnotes were made for better representation and accuracy.

11. STATISTICAL AND ANALYTICAL ISSUES

11.1 Data Capture and Management

11.1.1 Data Capture

The web-based survey was created by the (b) (4) programming team using (b) (4) software for web-based survey programming ((b) (4)). After the survey has been programmed and tested, the survey link and content were reviewed by a separate team within (b) (4) fielding operations group from the perspective of the respondent (i.e., the link was reviewed online and not within the (b) (4) software).

The data collected for this study was monitored for adherence with the Study Protocol ([Attachment 17.5](#)). All data were collected using a programmed web survey ([Attachment 17.4](#)). Prior to initiating the study, the appropriate edit programming was conducted to assure the final dataset required minimal cleaning of invalid responses. These programming procedures for the web-based survey data entry tool included response ranges, consistency checks, skip patterns, and other special edit procedures where applicable. At every step of data processing, results or creating grouping variables were cross-checked by (b) (4) operations team members who independently replicated the results and/or verified that the data had been handled appropriately and accurately. Any inconsistencies identified during this process were corrected before data were provided to (b) (4)'s analytical team to begin study analysis.

11.1.2 Data Management and Analysis QC Process

- Until the approval of the ZYN Patterns of Use SAP by SMNA, the data remained blinded and locked.

-
- Once the data were unlocked, the analytical team performed the following checks prior to conducting data analyses specified in the SAP:
 - The classification of participants into the study cohorts based on self-reported use or non-use of TNP was confirmed.
 - Completion of the survey was verified, and any respondent who did not complete the full survey was removed from analysis.
 - It was verified that respondents satisfied the inclusion and exclusion criteria.
 - The actual quota frequencies for each study cohort in the data set was compared against the quota frequencies specified in the Study Protocol. Any discrepancies were documented in the final report.
 - All variable coding followed as specified in the SAP (e.g., grouping age by age brackets, grouping the number of adults/children in the household, and total household income in the last 12 months).
 - All statistical analyses and results output were validated by another researcher on the analytical team for quality control. Validation covered:
 - Correct coding of variables.
 - Correct use of statistical methods as specified in the analysis section.
 - Correct export of results from SAS[®] output to Excel tables.

11.2 Missing Data

The structure of the Retrospective Study questionnaire did not have “true” missing data. The online survey did not allow respondents to proceed without receiving an answer to the present question. No partially completed surveys were included in the final Retrospective Study data set or Retrospective Study analyses. For the Retrospective Study, data points were either missing because the respondent selected “Don’t know” or “Decline to answer,” or they did not qualify to answer the question due to survey skip logic. Thus, these types of missing data were kept as-is and were reported descriptively (percentages and counts). The questionnaire was designed (and tested through cognitive interviewing) so that instructions were as easy to understand and as clear as possible, to help avoid missing data.

Both the Prospective Study and Retrospective Study questionnaires did not allow respondents to proceed without answering the present question. Hence, missing observations for completed daily or biweekly surveys arise because the respondent selected “Don’t know” or “Decline to answer,” or s/he did not qualify to answer the question due to prior answers. No modifications took place in these instances.

However, missing data in the Prospective Study could also arise from incomplete daily surveys. Study participants could remain in the study while failing to complete two daily surveys per week during the 10-week observational period, a policy utilized to allow flexibility for human inconsistency while maintaining a consistent flow of data pertaining to respondent usage. Data were absent in those situations; i.e., the investigator did not impute values. Daily TNP patterns of use outcomes, such as average daily use for each TNP for a respondent in a week, were calculated

based on the number of non-missing entries. Specifically, if 5 entries were available for a respondent in a given week, then the respondent's average daily use for each TNP for the week was based on the average of the 5 available entries. Likewise, if 6 entries were available for a respondent in a given week, then the respondent's average daily use for each TNP for the week was based on the average of the 6 available entries. (b) (4) of respondents (b) (4) of ZYN users and (b) (4) of non-users) did not have missing entries; (b) (4) (b) (4) of ZYN users and (b) (4) of non-users) missed at most 1 day a week; and (b) (4) (b) (4) of ZYN users and (b) (4) of non-users) missed 2 days a week. Therefore, even when respondents did have missing entries, most respondents missed only 1 day per week. On average, respondents completed 6.9 days per week (6.8 days among ZYN users and 6.9 days among non-users).

11.3 Data Checks During Fielding

The data collected for this study were monitored for adherence with the Study Protocol ([Attachment 17.5](#)). All data were collected using a programmed web survey ([Attachment 17.4](#)). Prior to initiating the study, appropriate edit programming was conducted to assure the final dataset requires minimal cleaning of invalid responses. These programming procedures for the web-based survey data entry tool included response ranges, consistency checks, skip patterns, and other special edit procedures where applicable. At every step of data processing, results or creating grouping variables were cross-checked by (b) (4) operations team members who independently replicated the results and/or verified that the data had been handled appropriately and accurately. Any inconsistencies identified during this process were corrected before data were provided to (b) (4)'s analytical team to begin study analysis.

Four (4) respondents in the Prospective Study contacted the (b) (4) operations team by phone to correct careless mistakes that were made while reporting product usage in their daily survey. Their answers were corrected for these questions, and subsequent ones following the skip pattern, before the analytical team began study analysis.

11.4 Identification of Outliers

When conducting online research, invariably some respondents will find a way to complete the survey without attempting to provide accurate, relevant responses. To ensure that those respondents did not compromise the integrity of the data, measures were taken to identify them in a systematic and objective way prior to actual analyses. No respondent was removed from the full study analyses. However, after performing all the data checks listed in the SAP guidelines ([Section 8.3 of SAP, Attachment 17.6](#)), outliers were identified, with the reason(s) being flagged listed below. Sensitivity analyses were conducted without these respondents to determine whether results differed from the full sample analyses.

- No respondents in the Retrospective Study were identified as outliers as specified by the procedures described in the SAP.
- (b) (4) respondents in the Prospective Study were identified as outliers because they:

-
- Were less than 4 SD below the mean or more than 4 SD above the mean for the number of products used (A1), number of each product used (A3), number of ZYN 6 mg pouches used (A5), or number of minutes typically kept ZYN pouches in mouth (A6); or
 - Demonstrated illogical responses for A3 and A5 (number of total and 6 mg ZYN pouches used). Illogical respondents were those who reported more 6 mg pouch use (A5) than their total ZYN pouch use (A3).

Per the ZYN Patterns of Use Study protocol ([Attachment 17.5](#)), respondents who participated in the Prospective Study were required to complete at least 5 daily surveys in each week in the 10-week observational period. Accordingly, respondents who missed more than 2 daily surveys in a given week were removed from the final locked data set, but were retained in a separate data set. Completion rate was (b) (4) for ZYN users and (b) (4) for non-users.

The results of the sensitivity analyses were reported ([Section 13.6](#)) as whether the exclusion of the outliers changed or did not change the statistical significance of each hypothesis from the full sample analyses.

12. STUDY RESPONDENTS

12.1 Study Fielding Summary

The fielding summary for number of respondents who entered the Retrospective survey, those who did not complete the survey, those who were terminated (and the reasons for termination) are summarized below.

(b) (4)



The fielding summary for number of respondents who entered the prospective survey are summarized below.

(b) (4)



12.2 Final Sample

There were (b) (4) participants who met the criteria for the Retrospective Study, (b) (4) ZYN users and (b) (4) ZYN non-users. The number of ZYN non-users was less than the proposed sample size from the SAP (b) (4), but the number of ZYN users exceeded the estimated amount substantially, making the total number of participants in the Retrospective Study greater than the original target (b) (4). The sample pool for both cohorts included participants from the 11 states where ZYN was commercially available, and the ZYN non-users were required to be current TNP users at the time of study entry. The Prospective Study included the participants from the Retrospective Study that agreed to continue and complied with the minimum of 5 responses per week for the entire 10 weeks of the study. The data was analyzed for (b) (4) ZYN users and (b) (4) ZYN non-users in the Prospective Study.

13. STUDY RESULTS

13.1 Descriptive Results

All respondents were included in the raw data descriptive results ([Attachment 17.1 Descriptive Retrospective Tables 1\(a&b\) – 13](#) and [Attachment 17.2 Descriptive Prospective Tables 1\(a-j\) - 11\(a-e\); Appendix 16.1](#))

13.2 Demographics and Respondent Characteristics

Within the study, researchers aimed to recruit a ZYN non-user group that was demographically similar to the ZYN user cohort recruited via on-pack stickers. Cohorts were similar in terms of geography, education, gender, and ethnicity, with a majority of respondents being white males. The largest discrepancies were observed in age, marital status, presence of children, and income.

[Table 3](#) contains the summary of all demographic data collected for the Retrospective Study.

Most of the participants for both cohorts responded that they had smoked at least 100 cigarettes in their lifetime (ZYN users=(b) (4), ZYN non-users=(b) (4)) ([Retrospective Descriptive Table 1a; Appendix 16.1; Attachment 17.1](#)).

Table 3: Socio-demographics of ZYN Users and ZYN Non-users.

(b) (4)



13.3 Results for Primary Objectives

13.3.1 Reported TNP Use in the Last 30 Days

Tables 4 and 5 summarize the statistical data of TNP usage in the last 30 days compiled from both ZYN users and non-users, and the statistical data for both cohorts' intention to quit all TNP respectively. Highlights from the data are as follows.

- ZYN users reported greater use of smokeless tobacco, versus cigarette smoking.
 - At a total U.S. level, (b) (4) of adults smoked cigarettes in 2016 ([Center for Disease Control and Prevention, 2018](#)), while (b) (4) of adults used smokeless tobacco in 2014 ([Center for Behavioral Health Statistics and Quality, 2015](#))
 - In the current study, with respect to cigarettes:
 - (b) (4) of ZYN users smoked cigarettes over the past 30 days, and only (b) (4) smoked every day.
 - Among ZYN non-users, (b) (4) smoked cigarettes during the past 30 days, (b) (4) every day.
 - Regarding moist snuff:
 - (b) (4) of ZYN users used moist snuff over the past 30 days, (b) (4) every day.
 - Among ZYN non-users, (b) (4) used moist snuff during the past 30 days, (b) (4) every day.
- Across all types of TNP (excluding ZYN itself), ZYN users expressed higher intent to quit versus ZYN non-users (with MTSS used to measure intent to quit.)

**Table 4: Primary Objective 1 - TNP Patterns of Use for ZYN Users and ZYN Non-users.
Reported TNP Use in the Last 30 Days.**

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)

**Table 5: Primary Objective 1 - TNP Patterns of Use for ZYN Users and ZYN Non-users.
Intention to Quit TNP Based on the MTSS.**

(b) (4)

(b) (4)



(b) (4)



(b) (4)



(b) (4)



13.3.2 Reported TNP Use in the Last 30 days Compared to Weeks Prior to Using ZYN

Table 6a summarizes the descriptive data of the combinations of TNP usage during the weeks prior to using ZYN:

- Prior to using ZYN, (b) (4) of ZYN users had previously used two or more TNP and (b) (4) had used 3 or more TNP.
- Prior to using ZYN, (b) (4) were mono-users.
- The most common combination of TNP use was moist snuff and snus ((b) (4)), followed by moist snuff and cigarettes ((b) (4)).

Table 6a: Primary Objective 2 – Among ZYN Users, Combinations of TNP Use During the Weeks Prior to Using ZYN.

(b) (4)



Table 6b summarizes the statistical data of TNP usage compiled from ZYN users over the last 30 days compared with TNP use prior to using ZYN. Highlights from the data are as follows.

- The median usage of ZYN before taking the retrospective survey was 5-6 months. Thus, respondents were likely comparing usage from roughly 6-7 months prior versus the most recent 30 days for the results below.
- The number of people who reported TNP use prior to using ZYN was in every case greater than the number of people who used TNP over the last 30 days. The percentages are determined from the total ZYN user cohort.
- Prior to using ZYN, (b) (4) of the users reported smoking cigarettes (b) (4) every day and (b) (4) some days).
 - In the last 30 days of using ZYN, only (b) (4) of the users reported smoking cigarettes (b) (4) every day and (b) (4) some days).
 - Accounting for the skip pattern of the questionnaire, which presented the question only to those who reported current use, these results suggest that over a hypothetical

period of 5-6 months and after introduction of ZYN, usage of cigarettes dropped by (b) (4).

- Use of other TNP from weeks prior to using ZYN to the last 30 days also declined.
- Prior to using ZYN, (b) (4) of the users reported using moist snuff (b) (4) every day and (b) (4) some days).
 - Over the last 30 days of using ZYN, only (b) (4) reported using moist snuff (b) (4) every day and (b) (4) some days).
 - Use of ZYN was associated with a (b) (4) reduction in the use of moist snuff.
- Usage of chewing tobacco was less frequent prior to using ZYN at (b) (4) (b) (4) every day and (b) (4) some days) than cigarettes and moist snuff.
 - Over the last 30 days of using ZYN, (b) (4) reported using chewing tobacco (b) (4) every day and (b) (4) some days).
 - Use of ZYN was associated with a (b) (4) reduction in the use of chewing tobacco.

Table 7b: Primary Objective 2 – Among ZYN Users, TNP Patterns of Use Over the Last 30 Days and TNP Patterns of Use During the Weeks Prior to Using ZYN.

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)




(b) (4)



(b) (4)



(b) (4)



13.3.3 ZYN Usage Compliance Over the Last 7 Days

Table 7 summarizes the statistical data of compliance with ZYN usage instructions compiled from ZYN users over the last 7 days. Highlights from the data are as follows.

- Generally speaking, ZYN users displayed compliance with suggested directions for product use.
- The two items where compliance was low were:

-
- 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 8: Primary Objective 3 - Compliance with ZYN Usage Instructions.

(b) (4)




(b) (4)



(b) (4)



(b) (4)



13.4 Results for Secondary Objective

13.4.1 Retrospective: Perceptions of Absolute Risk

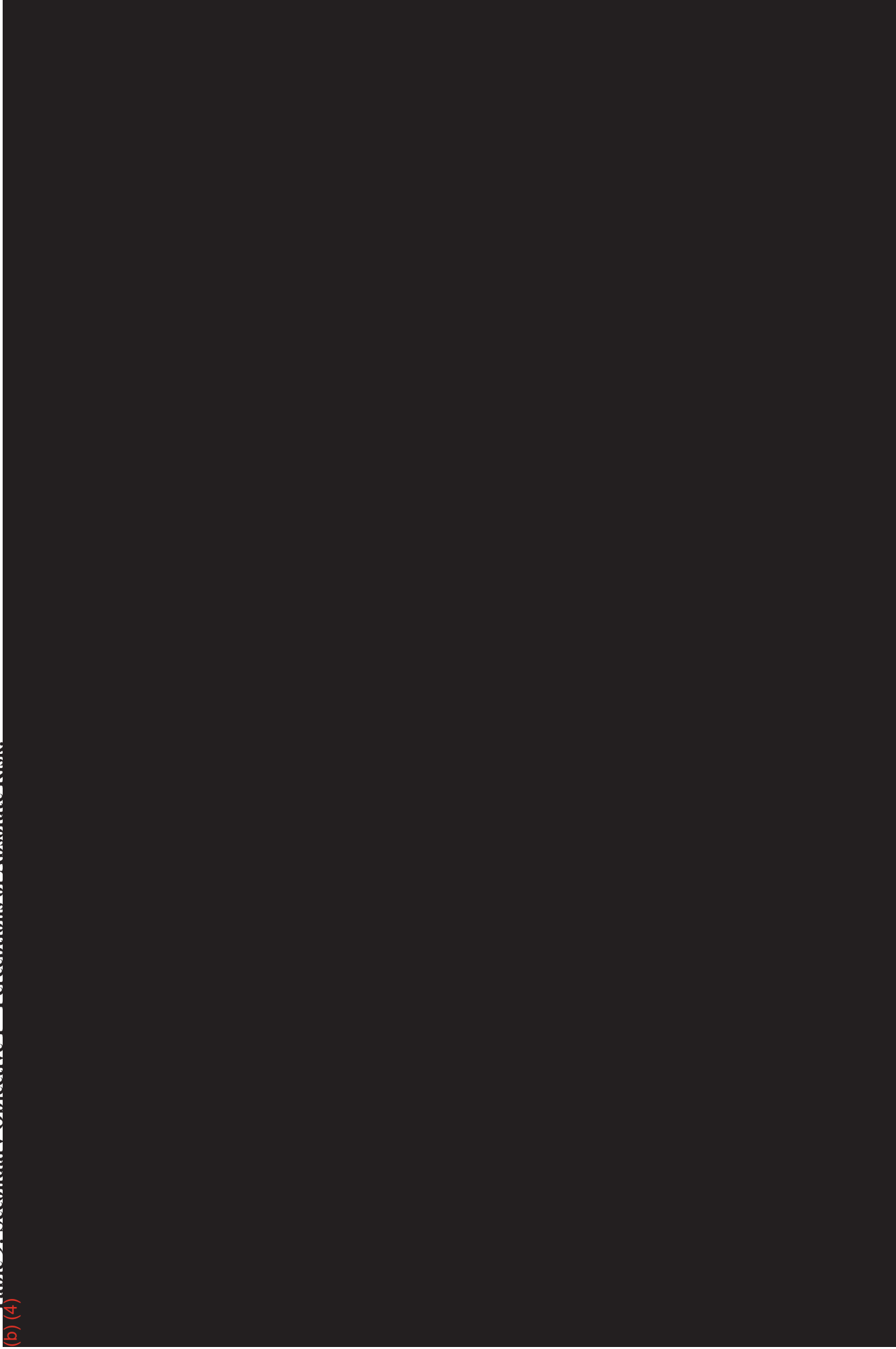
Table 8 summarizes the statistical data of perception of absolute risk of TNP use compiled from both cohorts. Highlights from the data are as follows.

- When evaluating the perception of absolute risk of TNP types, both ZYN users and non-users exhibited understanding of a continuum of risk when considering use of no TNP, ZYN (users only), and cigarettes.
- Specifically, respondents in both cohorts perceived absence of any TNP use having minimal health risks (very low-to-low) across all health conditions assessed (adult tooth loss, gum disease, mouth cancer, and serious health problems).

-
- Usage of ZYN was perceived as having a 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 of absolute health risks across both cohorts. In general, ZYN users perceived cigarettes to be more harmful than ZYN non-users.

Table 9: Secondary Objective 1 – Percentions of Absolute Risk.

(b) (4)



[REDACTED]

13.4.2 Retrospective: Perceptions of Relative Risk of ZYN to Other TNP

Table 9 summarizes the statistical data of perception of relative risk of ZYN use compared with other TNP compiled from ZYN users. Highlights from the data are as follows.

- Across health conditions, the majority of ZYN users perceived a much lower or a lower relative risk of daily use of ZYN compared with cigarettes, both ZYN and cigarettes, e-cigarettes, moist snuff, chewing tobacco, and snus.
- When comparing the relative risk of daily use of ZYN to aids to help stop smoking, the largest percentage of ZYN users perceived the same risk for all health conditions assessed.
- When comparing the relative risk of daily use of ZYN to never having used any TNP, the largest percentage of ZYN users perceived a higher risk for all health conditions investigated.

Table 10: Secondary Objective 2 – Among ZYN Users, Perceptions of the Relative Risk of ZYN.

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



13.4.3 Retrospective: Perceptions of Relative Risk of Adding ZYN to Existing TNP Usage.

Findings summarized in [Table 10](#) suggest that:

- Generally, ZYN is perceived to pose little additional risk to existing TNP use.
- Specifically, most ZYN users (slightly over (b) (4) across most products and conditions) perceived the same relative risk of the assessed health conditions when adding ZYN to existing TNP use as when not adding ZYN.
- About (b) (4) of ZYN users perceived a higher risk when adding ZYN to existing TNP; this varied depending on the specific TNP (i.e., 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.

Table 11: Secondary Objective 3 – Among ZYN Users, Perceptions of the Relative Risk of Adding ZYN to Existing TNP Use.

(b) (4)



(b) (4)



(b) (4)

(b) (4)

(b) (4)



(b) (4)

(b) (4)

(b) (4)

13.4.4 Retrospective: Perceptions of Relative Risk of Quitting All TNP Except ZYN to Quitting All TNP.

Across health conditions, when comparing the relative risk of quitting all TNP except ZYN versus quitting all TNP, respondents perceived continued ZYN usage (having quit all other TNP) as equally risky or of higher risk versus quitting TNP altogether, as shown in [Table 11](#).

Table 12: Secondary Objective 4 – Among ZYN Users, Perceptions of the Relative Risk of Quitting All TNP Except for ZYN Compared with Quitting All TNP.

(b) (4)



13.4.5 Prospective: Exploration of Daily TNP Patterns of Use Among ZYN Users and ZYN Non-users, Including Reasons for ZYN Use.

Tables 12 - 18 and Figures 1 - 3 describe the daily patterns of use of TNP among ZYN users and non-users. Highlights from the data are as follows.

- ZYN users continued to smoke fewer cigarettes than non-users. On average ZYN users smoked less than 1 cigarette per day versus the 8 per day observed in non-users over the 10-week period as described in Table 12.
 - Figure 1 depicts a trend towards decreasing the number of cigarettes and amount of moist snuff used among ZYN users.
 - Figure 1 depicts a similar trend of number of cigarettes smoked among non-users, however this was not observed with moist snuff.
- The number of participants 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 (cigarettes: (b) (4); moist snuff: (b) (4)) to week 10 (cigarettes: (b) (4); moist snuff: (b) (4)).
- Among ZYN non-users, percentage of cigarettes smokers per week remained consistent over the 10 weeks. (Table 14; Figure 2).
 - Although based on a small sample size, numerically the number of smokers among ZYN users trended downward during the 10 weeks. This trend would corroborate the decline in actual cigarettes smoked.
- Moist snuff usage among ZYN non-users trended from (b) (4) (week 1) to (b) (4) (week 10; Table 14; Figure 2).
- The majority of ZYN users reported that one reason for using ZYN was to reduce (b) (4) in week 10) or to help quit cigarette use ((b) (4) in week 10) (Table 18), which was supported by the diary data.
- The percentage of respondents that reported using ZYN-only increased throughout the study from week 1 to week 10, and the percentage that used other TNP decreased (Table 15; Figures 3 and 4).
- ZYN users also reported little desire to quit use of ZYN (Table 16), although the percentage that did not use ZYN at all increased from (b) (4) in week 1 to (b) (4) by week 10 (Table 15).
- The most commonly reported reasons for using ZYN were the following (note that respondents could select more than one reason):
 - *To help reduce or quit cigarette smoking;*

-
- *to use in environments where other TNP were inappropriate or not allowed;*
 - *less harmful than other TNP;*
 - *to avoid spitting;*
 - *flavor options;*
 - *to not smell like tobacco/smoke;*
 - *more acceptable to non-tobacco users;*
 - *no one can tell it is being used;*
 - *and the ease of use.;*
 - Of the aforementioned reasons, *to help reduce cigarette smoking, use in environments where other TNP were inappropriate/not allowed, less harmful than cigarettes, no one can tell it is being used,* and *the ease of use* increased in percentage over the course of the 10 weeks ([Table 18](#)).
 - Intention to quit e-cigarettes increased among ZYN users at a higher rate than ZYN non-users.

Table 13: Secondary Objective 5 - TNP Patterns of Use Among ZYN Users and ZYN Non-Users Based on the Average Daily Reported TNP Use for Each Week in Prospective Observational Period.

(b) (4)



(b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Figure 1: Secondary Objective 5 - TNP patterns of use among ZYN users and ZYN non-users based on the average daily reported TNP use for each week in prospective observational period.¹



Table 14: Secondary Objective 5 - TNP Patterns of Use Among ZYN Users and ZYN Non-Users Using TNP Every Day Based on Weekly Use in the Prospective Observational Period.

(b) (4)











Table 15: Secondary Objective 5 - TNP Patterns of Use Among ZYN Users and ZYN Non-Users Using TNP Every Day or Some Days Based on Weekly Use in the Prospective Observational Period.

(b) (4)







(b) (4)

(b) (4)



Figure 2: Secondary Objective 5 - TNP patterns of use among ZYN users and ZYN non-users using TNP every day or some days based on weekly use in the prospective observational period.



Table 16: Secondary Objective 5 - TNP Patterns of Use Among ZYN Users, Percent of ZYN Users Using ZYN with Other TNP.

(b) (4)

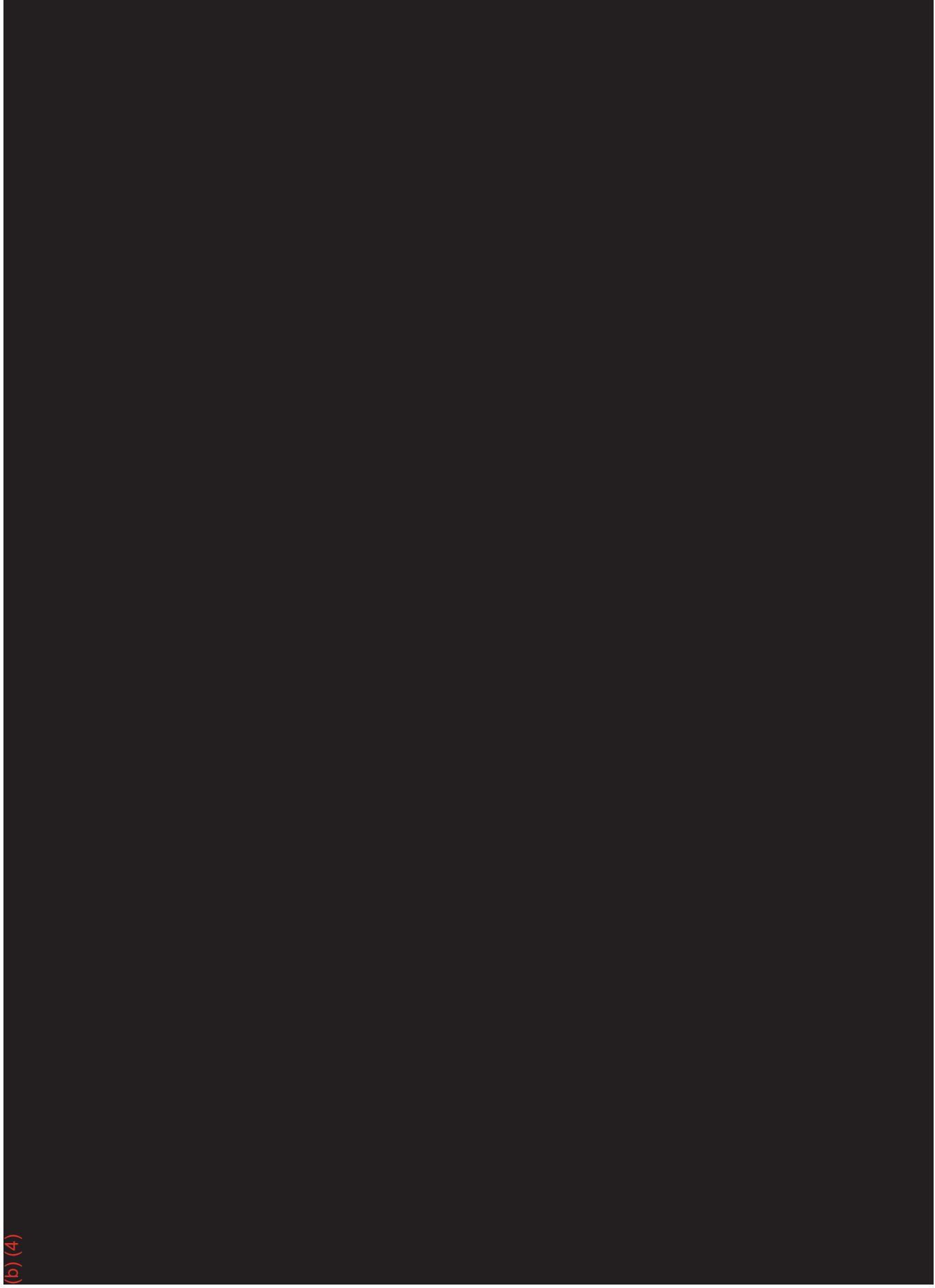




Figure 3: Secondary Objective 5 - TNP patterns of use among ZYN users, percent of ZYN users using ZYN with other TNP.

(b) (4)



Figure 4: Secondary Objective 5 - TNP patterns of use among ZYN users, percent of ZYN users using ZYN with smokeless TNP.



Table 17: Secondary Objective 5 - TNP Patterns of Use Among ZYN Users and ZYN Non-users, Intention to Quit TNP During the Prospective Observational Period Based on the MTSS.

(b) (4)







[REDACTED]

[REDACTED]

Table 18: Secondary Objective 5 – TNP Patterns of Use Among ZYN Users During the Prospective Observational Period. Outcomes Include Percent of Days That ZYN is Used, Average Number of ZYN Pouches Used Per Day, and Average Number of Minutes ZYN was Kept in the Mouth.

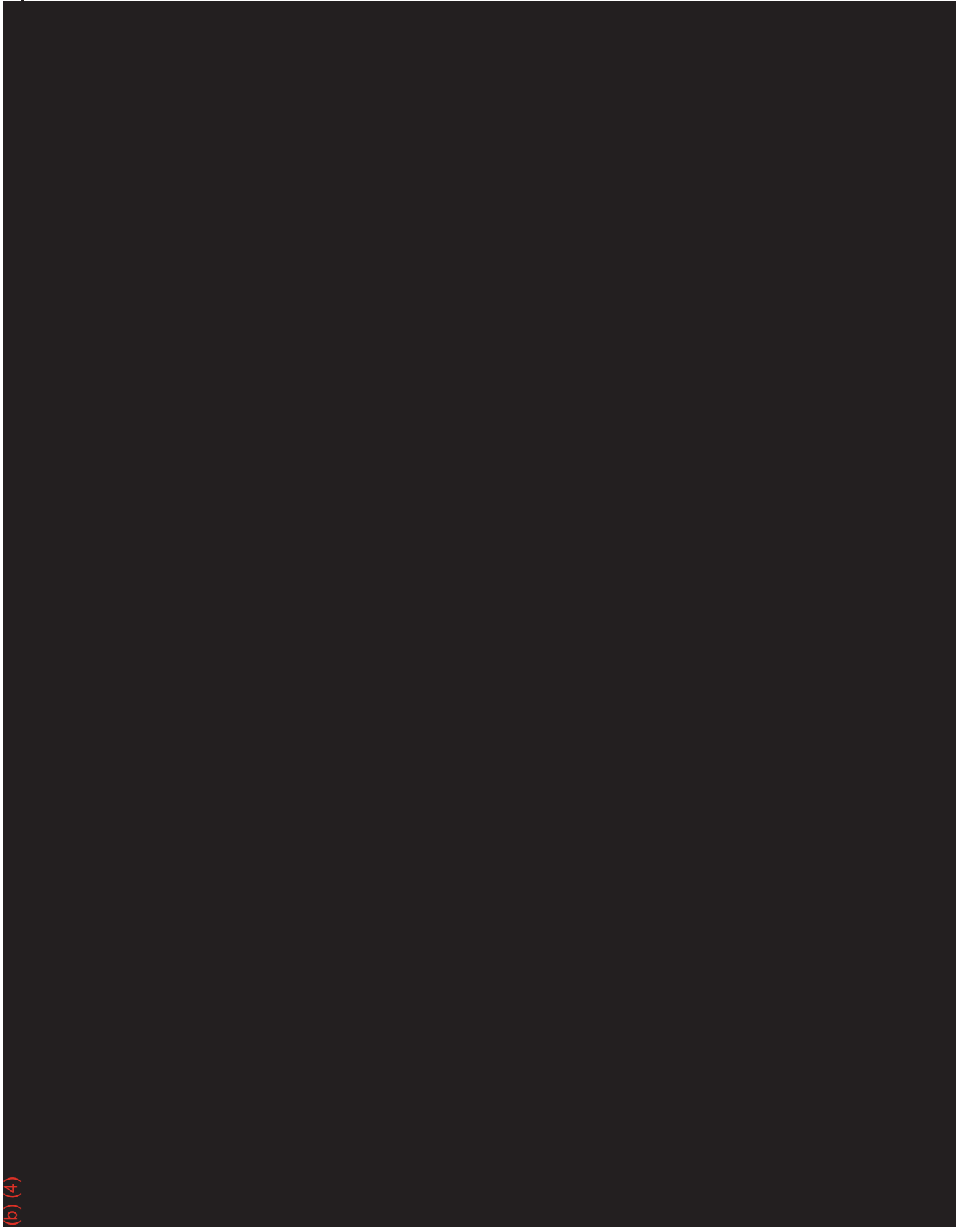
(b) (4)



Table 19: Secondary Objective 5 – Among ZYN Users, Reasons for Using ZYN.

(b) (4)











(b) (4)



13.4.6 Prospective: Comparison of the Tendencies of ZYN Users to Quit TNP or in Complete Substitution of Other TNP.

Quitting was defined as recording zero TNP use of any kind in weeks 9 and 10. Complete substitution was defined as starting the prospective study using ZYN and another TNP, but recording use of only ZYN in weeks 9 and 10 (Table 19). By weeks 9 and 10, (b) (4) of ZYN users reported completely substituting ZYN in place of other TNP. Additionally, a small proportion of ZYN users and non-users reported quitting all TNP by weeks 9 and 10, (ZYN users: (b) (4); non-users: (b) (4)).

Table 20: Secondary Objective 6 - Among ZYN Users and ZYN Non-users, Quitting All TNP Use at the End of the Prospective Observational Period, and Completely Substituting Other TNP for ZYN.

(b) (4)



13.5 ZYN Preferences in Retrospective Study

Although not a primary or secondary endpoint, the Retrospective Study evaluated the product preferences of the ZYN user cohort. 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, at (b) (4) and (b) (4) respectively. Coffee was the least popular flavor at only (b) (4). The strongest nicotine strength (6 mg) was most commonly used by (b) (4) of the cohort, with (b) (4) of respondents reporting they used 6 mg all the time. Table 20 is a selected representation of Retrospective Descriptive Table 4 (Appendix 16.1; Attachment 17.1).

Table 21: Flavor of ZYN/Nicotine Strength of ZYN/Duration of Using ZYN/Proportion of ZYN Usage with 6 mg Nicotine Strength.

(b) (4)



(b) (4)



13.6 Results for Sensitivity Analyses

Sensitivity analyses were conducted for every outcome with the outliers removed ([Attachment 17.3 Statistical Tables 21S – 28S](#), [Appendix 16.1](#)) in the prospective study. The results of the sensitivity analyses for the prospective study demonstrated that the exclusion of the outliers did not affect the original descriptive results in a substantive way.

13.7 Adverse Events

13.7.1 Passive Adverse Event Surveillance

(b) (4) and Swedish Match implemented Adverse Event (AE) surveillance in a passive mode for this study. Only unsolicited AEs or product complaints spontaneously reported by study participants or on their behalf were collected. All reported AEs were assessed by a Health Care Professional (HCP).

An AE includes:

1. Any event which started anytime during the study, from the time the Informed Consent Form (ICF) was completed, through the end of the data collection period.
2. Any pre-existing health condition which worsened during the study.

13.7.2 Participant Access and Call Handling

A call center, managed by (b) (4) was made available to study participants for the purposes of reporting any technical difficulties related to completing any surveys within the project, asking questions about the study, and reporting AEs if they were to occur. To encourage proactive communication from participants, a call center toll free number was communicated to participants in three ways:

1. The number was shown on the ICF and on every page of the online Retrospective study.

-
2. The number was shown on the ICF and the introduction to the online e-diary study.
 3. The number was shown every day on the first screen of the online e-diary study.

When participants called into (b) (4), the call center answered as the “Market Research Call Center.” If the call involved an AE, the process according to the AE Management plan was followed. If the call was concerning a product complaint, information was first gathered for reporting, and then the caller was given the option of being transferred to or placing a direct call to Swedish Match’s consumer contact center (Phone: 270-685-8777). Participants were also given the option of contacting Swedish Match via the product website, ZYN.com. The participants were given the option to decline to speak to Swedish Match’s consumer contact center. Instructions were provided to Swedish Match’s call center (Phone: 270-685-8777) in case a study participant contacted that group with study-related questions, in which case they were referred back to (b) (4) as appropriate.

There were instances when the call center reached out directly to a study participant; for example, participants who were at risk of being disqualified due to missing too many days of e-diary completion received reminder calls from (b) (4). Among all respondents who completed the 10 weeks, 348 respondents (228 ZYN users and 120 non-users) required at least one reminder call. The average number of calls made to a ZYN user for reminders was 5 (minimum=1, maximum=25), and 6 (minimum=1, maximum=21) to a non-user.

13.7.2.1 Involved Parties

The parties involved in the study and surveillance were:

- Swedish Match, sponsor of the (b) (4).
- (b) (4), the contract research agency executing the (b) (4).
- (b) (4), operating the study call center, supervised by (b) (4).
- (b) (4) managing the AE case processing for the study participants, supervised by (b) (4).

13.7.3 AE Report Summary

A total of 2 non-serious AEs were received, with no follow up required.

13.7.4 Product Complaints Report Summary

A total of 1 product complaint was received with no follow up required.

13.7.5 Product Complaint Line Listing and Summary

As outlined in the AE Management Plan, a cumulative product complaint line listing and summary which may be reported to the FDA can be viewed in [Attachment 17.8](#). All information has been previously provided to Swedish Match as noted in the Product Complaint Report Summary ([Attachment 17.9](#)).

13.8 Results Summary

Demographics and Respondent Characteristics:

Within the study, researchers aimed to recruit a ZYN non-user group that was demographically similar to the ZYN user cohort recruited via on-pack stickers. Cohorts were similar in terms of geography, education, gender, and ethnicity, with a majority of respondents being white males. The largest discrepancies were observed in age, marital status, presence of children, and income.

Primary Objective 1: Reported TNP use in the Last 30 Days

ZYN users mainly used smokeless tobacco products, while the ZYN non-user segment predominantly comprised smokers. ZYN users expressed much clearer intention to quit use of tobacco products (excluding ZYN, measured using the Motivation to Stop Smoking scale [MTSS]) compared with ZYN non-users.

Primary Objective 2: Reported TNP Use in the Last 30 Days Compared to Weeks Prior to Using ZYN.

Median usage of ZYN before taking the retrospective survey was 5-6 months. Thus, respondents were likely comparing usage from roughly 6-7 months prior versus the most recent 30 days, for the results below.

Prior to using ZYN, more than (b) (4) of ZYN users used a combination of multiple TNP with moist snuff and snus being the most common combination, followed by moist snuff and cigarettes.

Prior to using ZYN, (b) (4) of the user cohort reported smoking cigarettes (b) (4) every day and (b) (4) some days). However, in the last 30 days of using ZYN, only (b) (4) of the user cohort reported smoking cigarettes (b) (4) every day and (b) (4) some days). This finding suggests that over a hypothetical period of 5-6 months, usage of cigarettes dropped by (b) (4).

In addition to smoking, absolute use and frequency of use of other TNP from weeks prior to using ZYN to the last 30 days also declined. Prior to using ZYN, (b) (4) of the ZYN-user cohort reported using moist snuff (b) (4) every day and (b) (4) some days). However, in the last 30 days of using ZYN, only (b) (4) of the user cohort reported using moist snuff (b) (4) every day and (b) (4) some days). Prior to using ZYN, (b) (4) of the user cohort reported using chewing tobacco (b) (4) every day and (b) (4) some days). Chewing tobacco usage also declined in the last 30 days of using ZYN, with (b) (4) reporting use (b) (4) every day and (b) (4) some days).

Primary Objective 3: ZYN Usage Compliance over the Last 7 Days

Generally, ZYN users reported compliance with suggested directions for product use. The two items where compliance was low were (a) duration of usage and (b) placement of ZYN pouch in the mouth. First, 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 mins, per instruction, whereas (b) (4) reported that they always do. Second, (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.

Secondary Objective 1 (Retrospective): Perceptions of Absolute Risk

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, and cigarettes. Specifically, respondents perceived the absence of any TNP use as having minimal health risk, usage of ZYN as having low-to-moderate health risk (ZYN users only), and cigarette smoking as having moderate-to-very high risk.

Secondary Objective 2 (Retrospective): Perceptions of Relative Risk of ZYN to Other TNP

When evaluating relative risk of TNP types and usage scenarios, ZYN users exhibit an understanding of a continuum of risk when considering the use of ZYN compared with a variety of TNP options. Compared with cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, and dual use of ZYN and cigarettes, ZYN users perceived a lower relative risk of daily use of only ZYN. When comparing the relative risk of daily use of ZYN to aids to help stop smoking or never having used any TNP, respondents perceived ZYN as being equally risky or of higher risk, respectively.

Secondary Objective 3 (Retrospective): Perceptions of Relative Risk of Adding ZYN to Existing TNP Usage.

Findings suggest that generally, ZYN is perceived to pose little additional risk to existing TNP use. Specifically, a majority of ZYN users (just over (b) (4)) perceived the same risk of health conditions when adding ZYN to existing TNP relative to not adding ZYN. About (b) (4) of ZYN users perceived a higher risk when adding ZYN to existing TNP; results varied depending on the specific TNP (e.g., 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.

Secondary Objective 4 (Retrospective): Perceptions of Relative Risk of Quitting All TNP Except ZYN to Quitting All TNP.

Across health conditions, when comparing the relative risk of quitting all TNP except ZYN versus quitting all TNP, respondents perceived continued ZYN usage (having quit all other TNP) as equally risky or of higher risk versus quitting TNP altogether.

Secondary Objective 5 (Prospective): Exploration of Daily TNP Patterns of Use Among ZYN Users and ZYN Non-users, Including Reasons for ZYN Use.

ZYN users reported smoking substantially fewer cigarettes than non-users. The number of respondents who reported smoking cigarettes every day or some days dropped among ZYN users throughout the study, whereas cigarette use remained consistent among ZYN non-users.

Further, the percentage of participants who smoked cigarettes every day or some days (defined as at least 1 day a week) decreased for ZYN users from week 1 ((b) (4)), to week 10 ((b) (4)). In contrast, no change was observed for ZYN non-users throughout the 10 weeks. In summary, smokers who used ZYN reported fewer days smoking at least one cigarette than non-users. These findings are consistent with ZYN users' intention to quit cigarettes, as assessed with MTSS. The majority of ZYN users reported that their reason for using ZYN was to reduce or to help quit cigarette use, which was supported by the diary data.

Similar to cigarettes, we observed a pattern of decreasing use of moist snuff. Specifically, ZYN users' use of moist snuff everyday and some days dropped from ((b) (4)) (week 1) to ((b) (4)) (week 10). The reduction in moist snuff usage among ZYN non-users was less steep; ((b) (4)) (week 1) to ((b) (4)) (week 10). Considering these results in context, many ZYN users entered the prospective study having used ZYN for a substantive length of time; median usage = 5-6 months. Arguably, their usage habits were established and consistent by the time they began day 1 of the prospective study. Evidence from the retrospective data supports that switching/quitting from other TNP had already occurred prior to starting the prospective study. Therefore, seeing evidence of continual reduction in cigarette and other TNP usage during the 10-week prospective period is noteworthy.

There was no observed difference in the daily number of pouches of ZYN used, the duration of each pouch's use, or the number of respondents reporting use of ZYN everyday throughout the 10-week period. Although there was a slight decrease in the number of reported participants who used ZYN every day or some days, the number of participants that reported using **ZYN only** increased throughout the Prospective Study. ZYN users also reported little desire to quit use of ZYN, although the percentage that did not use ZYN at all increased across the 10 weeks ((b) (4)) in week 1 to ((b) (4)) in week 10). The most common reasons for using ZYN at the end of the 10 weeks were: *to help reduce/quit cigarette smoking; to use in environments where other TNP were inappropriate/not allowed; less harmful than cigarettes; no one can tell it is being used; and ease of use.*

Secondary Objective 6 (Prospective): Comparison of the Tendencies of ZYN Users to Quit TNP or in Complete Substitution of Other TNP.

By weeks 9 and 10, ((b) (4)) of ZYN users reported completely substituting ZYN in place of other TNP and ((b) (4)) of ZYN users had quit all TNP.

14. DISCUSSION AND OVERALL CONCLUSIONS

The principal research questions, “How do ZYN users and ZYN non-users use TNP?” and “How do they perceive health risks associated with TNP?” were investigated by means of a retrospective assessment (the Retrospective Study), as well as a 10-week prospective study among ZYN users and ZYN non-users (the Prospective Study) in the ZYN Patterns of Use Study.

14.1 Strengths and Limitations of the Study

This study was conducted based on fundamental social and statistical science, with valuable guidance by the Center for Tobacco Products (CTP [Addendum, 2017](#)), to evaluate the risks and benefits to the population, including users and non-users of the tobacco product.

The resulting study featured many strengths. The study benefitted from the substantial number of ZYN users recruited through the on-pack invitations, a number higher than the original target. Continuation of participants in the Prospective Study exceeded expectations, and compliance was high once entered. Additionally, the use of qualitative cognitive interviews prior to the execution of the quantitative survey strengthened the design of the web-based survey. Cognitive interviews ensured that the materials were appropriate and sufficiently clear to respondents. The study results were robust enough to withstand the inclusion of outliers. As the pattern of results were the same in the full sample analysis and the sensitivity analysis (conducted for prospective study), it appeared that the inclusion of outliers did not have a substantive impact on the findings.

Finally, in virtually all cases, survey questions utilized validated scales, or scales directly comparable to studies in literature. In particular, usage of the MTSS allowed for simple, justifiable interpretation. Scales used in risk perception questions line up with other tobacco-related research, such as HINTS.

There were several limitations to the current study, none of which should draw concern regarding data integrity. Although we attempted to match the ZYN non-user cohort to the ZYN user cohort, smoking incidence (30 days before using ZYN for ZYN users) differed across these cohorts and was higher among non-users. ZYN users in our study were likely to be relatively established in their use of ZYN, and therefore, we might be underestimating baseline cigarette use that would have been seen among those who just began using ZYN. Both the retrospective and prospective data from this study were dependent on respondent self-reporting, and subsequently reported variables may be subject to recall bias or attempts at appeasement of the investigators. Self-reported data collection is a standard approach, and any potential problems with recall bias were anticipated to be constant across time points. Also, the inclusion of a robust sample size helps alleviate some of these concerns.

Researchers could not analyze respondents who responded, “don’t know” or “decline to answer”. As in prospective clinical studies, we set evaluability rules; as such, those who responded “don’t know” or “decline to answer” were excluded from the evaluable subset of responders, which was the primary population for analyses.

While driven by best practice and highest likelihood of obtaining enough of the right respondents, recruitment methods for ZYN users and non-users were not consistent. ZYN users were recruited from stickers placed on ZYN cannisters. The ZYN non-users were recruited utilizing online consumer survey panels with supplements from a call center, with recruitment criteria based on the demographics represented in the ZYN user cohort. Even with efforts to ensure a representative sample using stratification, the precise proportion of subgroups in the study sample could not be completely controlled. In fact, regardless of how respondents were recruited, the possibility exists that the people who declined the opportunity to participate in the research may differ in a systematic way from the people who accepted the opportunity.

14.2 Overall Conclusions

Conclusion: The Patterns of Use study was a two-part observational study intended to assess the differences in usage of TNP between ZYN users and non-users, intention to quit TNP, compliance, and perceptions of risk. The first part of the study, “Retrospective”, evaluated past usage of TNP (before and after ZYN), compared TNP use between ZYN users and non-users, assessed intention to quit TNP, and evaluated perceptions of risk. The second part of the study, “Prospective”, monitored the continued use of TNP and intention to quit TNP in a 10-week period among a subgroup of the Retrospective study respondents.

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 that:

- 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.

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- The number of days per week ZYN was used slightly decreased over the 10 weeks, although the number of pouches 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.

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16. APPENDICES

16.1 Tables

Table 22: SAP Tables

Table Number	Title
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(b) (4)

Table Number	Title
(b) (4)	

Table 23: Retrospective Descriptive Tables

Table Number	Title
(b) (4)	

Table 24: Prospective Descriptive Tables

Table Number	Title
(b) (4)	

Table 25: Sensitivity Tables (Prospective Study)

Table Number	Title
(b) (4)	