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STATISTICAL ANALYSIS PLAN

ZYN® Likelihood of Use

Swedish Match North America

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Statistical Analysis Plan

ZYN® Likelihood of Use Study

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Status: Approved

Date: 6 June 2018

Prepared by: (b) (4)

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Swedish Match North America, its parent and affiliate companies

(b) (4)

(b) (4)

TABLE OF CONTENTS

LIST OF TABLES	3
1. LIST OF ABBREVIATIONS AND DEFINITIONS	4
2. RESPONSIBLE PARTIES	5
2.1 Investigator and Contributors	5
2.2 Sponsor	5
3. STATISTICAL ANALYSIS PLAN (SAP) AMENDMENTS AND UPDATES	5
4. BACKGROUND AND RATIONALE.....	6
5. OBJECTIVES	6
5.1 Primary Objectives.....	7
5.2 Secondary Objectives.....	7
6. Overall Study Design.....	8
6.1 Study Design.....	8
6.2 Study Cohorts.....	9
6.2.1 Subject Selection: Inclusion Criteria	9
6.2.2 Subject Selection: Exclusion Criteria	9
6.3 Precision Analysis.....	11
6.4 Study Sample Size	12
6.5 Variables of Relevance to the Study	13
6.5.1 Outcomes	13
6.5.2 Additional Variables of Interest.....	23
7. STATISTICAL ANALYSIS	24
7.1 Presentation of Analysis Results.....	24
7.2 Study Analysis	24
7.3 Socio-demographics and Comprehension Check	25
7.4 Primary Objectives.....	25
7.5 Secondary Objectives.....	26
8. STATISTICAL AND ANALYTICAL ISSUES	36
8.1 Data Capture and Management.....	36
8.1.1 Data Capture	36
8.1.2 Data Management and Analysis QC Process.....	36
8.2 Handling of Missing Data.....	37
8.3 Identification of Outliers.....	37
9. REFERENCES	39
10. TABLE SHELLS	40

(b) (4)

(b) (4)

LIST OF TABLES

Table 1. Study Cohorts.	10
Table 2. Sample sizes for the ZYN® Likelihood of Use Study.	12
Table 3. Outcomes Table for Primary Objective 1 – Impacts of ZYN® on Perceptions and Intentions Related to the use of TNP.	16
Table 4. Outcomes Table for Primary Objective 2 – Appeal of Various ZYN® Brand and Product Attributes.....	18
Table 5. Outcomes Table for Secondary Objective 1 – Perceptions of Absolute Risk.	19
Table 6. Outcomes Table for Secondary Objective 2 – Perceptions of Relative Risk.	20
Table 7. Analysis Table for Primary Objective 1 – Impacts of ZYN® on Perceptions and Intentions Related to the use of TNP.	27
Table 8. Analysis Table for Primary Objective 2 – Appeal of Various ZYN® Brand and Product Attributes.....	29
Table 9. Analysis Table for Secondary Objective 1 – Perceptions of Absolute Risk.	30
Table 10. Analysis Table for Secondary Objective 2 – Perceptions of Relative Risk.....	32
Table 11. Socio-demographic and Comprehension Check Variables for all study participants.	40
Table 12. Table Shell for Primary Objective 1 – Likelihood to Initiate or Reinitiate TNP.....	45
Table 13. Table Shell for Primary Objective 1 – Current Use of TNP among TNP Users.	47
Table 14. Table Shell for Primary Objective 1 – Future Intention to Buy ZYN® among TNP Users.	53
Table 15. Table Shell for Primary Objective 1 – Future Intention to Use Current TNP after Exposure to ZYN®.	54
Table 16. Table Shell for Primary Objective 1 – Current Intention to Quit TNP and Future Intention to Quit TNP.....	61
Table 17. Table Shell for Primary Objective 2 – Appeal of ZYN® Brand and Product Attributes.....	64
Table 18. Table Shell for Secondary Objective 1 – Perceptions of Absolute Risk to a Person who Smokes Cigarettes Every Day but Uses no Other Tobacco Products.....	69
Table 19. Table Shell for Secondary Objective 1 – Perceptions of Absolute Risk Associated With Never Having Used any TNPs.	73
Table 20. Table Shell for Secondary Objective 1 – Perceptions of Absolute Risk Associated Using Only ZYN® Daily.	77
Table 21. Table Shell for Secondary Objective 2 – Perceptions of Relative Risk of Adult Tooth Loss.	81
Table 22. Table Shell for Secondary Objective 2 – Perceptions of Relative Risk of Gum Disease....	89
Table 23. Table Shell for Secondary Objective 2 – Perceptions of Relative Risk of Mouth Cancer. .	97
Table 24. Table Shell for Secondary Objective 2 – Perceptions of Relative Risk of Serious Health Problems.	105

(b) (4)

1. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definition
CTP	Center for Tobacco Products
FDA	Food and Drug Administration
HINTS	Health Information National Trends Survey
MTSS	Motivation to Stop Scale
Non-users	Never and Former users of tobacco/nicotine products
PATH	Population Assessment of Tobacco and Health
PMTA	Premarket Tobacco Product Application
Respondents	Total sample which includes current, never, and former users of tobacco/nicotine products
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SMNA	Swedish Match North America
TNP	Tobacco/Nicotine Product
U.S.	United States
vs.	Versus

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2. RESPONSIBLE PARTIES

2.1 Investigator and Contributors

Investigator:

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Project Team:

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2.2 Sponsor

Swedish Match North America

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3. STATISTICAL ANALYSIS PLAN (SAP) AMENDMENTS AND UPDATES

Number	Date	Section of SAP	Amendment or Update	Reason
1	06/06/2018	Table shells	Amendment	Format edits to the table shells and accompanying footnotes were made for better representation and accuracy.
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(b) (4)

4. BACKGROUND AND RATIONALE

In 2009, the Family Smoking Prevention and Tobacco Control Act was signed into law, giving the FDA the power to regulate the tobacco industry and establishing the Center for Tobacco Products (CTP) within the FDA. This law gives the CTP authority to regulate the marketing/advertising content and sale of tobacco/nicotine products^a (TNP). The FDA requires that the marketing of a new tobacco product is appropriate for the protection of the public health as determined “on the basis of well-controlled investigations” (Section 910).¹

The CTP has provided draft guidance on data for human studies designed to evaluate the risks and benefits to the population as a whole, including users and non-users of the tobacco product.^{1,2} In making this evaluation the FDA will assess the product under review and take into account (1) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (2) the increased or decreased likelihood that those who do not use tobacco products will start using such products.¹ This evidence must be submitted for all currently marketed products as part of a premarket tobacco product application (PMTA). Products marketed in the U.S. after February 15, 2007 must obtain a marketing authorization through a PMTA application or they can no longer be sold in the U.S.^{1, 2}

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. As a result of the Tobacco Control Act requirements, SMNA must submit a PMTA to continue marketing the ZYN[®] product. The output of this research will be submitted to the FDA as part of the ZYN[®] PMTA.

5. OBJECTIVES

The overarching research question within the ZYN[®] Likelihood of Use Study can be stated as follows: *(i) How does exposure to the ZYN[®] description and packaging label affect intentions, behaviors, and perceptions of TNP users and TNP non-users, when compared pre- to post-exposure, and (ii) how does exposure to the ZYN[®] description and packaging label have a different impact on intentions, behaviors, and perceptions across TNP user and TNP non-user groups?* These questions will be evaluated by way of an observational study with a pre-/post-exposure design. No formal hypotheses are specified for the ZYN[®] Likelihood of Use Study.

^a “Tobacco/nicotine products” (TNP) refers to any combination of the following products: 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. This list of tobacco/nicotine products defining TNP is based on the Population Assessment of Tobacco and Health.

(b) (4)

5.1 Primary Objectives

1. Among all respondents, assess whether being exposed to a ZYN[®] description and packaging label impacts perceptions and intentions related to the use of TNP.
 - i. Among TNP never-users legal age to 24, TNP never-users older than 24, and former TNP users evaluate:
 - Current likelihood to initiate or reinstate TNP based on intention to buy TNP
 - Future likelihood to initiate or reinstate TNP based on intention to buy ZYN[®] after being exposed to a ZYN[®] description and packaging label
 - ii. Among cigarette smokers with intent to quit, cigarette smokers without intent to quit, and current tobacco users (excluding cigarettes) evaluate:
 - Current use of TNP
 - Future intention to buy ZYN[®] after being exposed to a ZYN[®] description and packaging label
 - Future intention to use current TNP after being exposed to a ZYN[®] description and packaging label
 - iii. Among cigarette smokers with intent to quit, cigarette smokers without intent to quit, and current tobacco users (excluding cigarettes) evaluate:
 - Current intention to quit use of TNP
 - Future intention to quit use of TNP after being exposed to a ZYN[®] description and packaging label
2. Among all respondents, measure the appeal of various ZYN[®] brand and product attributes after being exposed to a ZYN[®] description and packaging label. Attributes include:
 - i. Overall look and feel;
 - ii. Variety of flavors;
 - iii. Product design;
 - iv. Physical product;
 - v. Child-safety lid.

5.2 Secondary Objectives

1. Among all respondent cohorts, explore variation in perceptions of absolute risk associated with never having used any TNP, smoking cigarettes, and using ZYN[®].
 - i. Measurement of absolute risk of non-usage and smoking to occur prior to showing respondents the ZYN[®] description and packaging label.
 - ii. Measurement of absolute risk of ZYN[®] to occur after showing respondents the ZYN[®] description and packaging label.

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(b) (4)

The health conditions under consideration when considering absolute risk are:

- Adult tooth loss
- Gum disease
- Mouth cancer
- Serious health problems

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

- i. Using other tobacco products;
- ii. Using aids to help stop smoking;
- iii. Quitting all TNP; and
- iv. Never using any TNP.

All measurements of relative risk will be collected after respondents are exposed to the ZYN® description and packaging label.

The health conditions under consideration when considering relative risk are:

- Adult tooth loss
- Gum disease
- Mouth cancer
- Serious health problems

6. OVERALL STUDY DESIGN

6.1 Study Design

The ZYN® Likelihood of Use Study consists of a pre-/post-exposure, repeated measures study design. Study participants will be exposed to the ZYN® description and packaging label, which will provide a picture of the canister and a schematic of the label for the top, bottom, and side of the canister. The ZYN® description and packaging label will indicate product information, including instruction on use, strengths, number of pouches in canister, and flavors, as well as the required warning that nicotine is an addictive chemical.

Data for the ZYN® Likelihood of Use Study will be obtained using responses from a customized web-based survey of invited consumers who meet inclusion and exclusion criteria (explained in [Section 6.2.1](#) and [Section 6.2.2](#)), and who agree to participate. Consumers will initially be recruited from verified online consumer survey panels, including (b) (4)

. If these panels do not satisfy sampling needs, we will expand and include other panels such as (b) (4). Study recruitment will result in a representative sample (based on U.S. Census data and including age, gender, geographic region, racial or ethnic background, and education) to be utilized in the study. The study sample will then be recruited from the invited sample using a stratified sampling framework, based on socio-demographic characteristics of the adult

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population from the Population Assessment of Tobacco and Health (PATH) study.³ The overall recruitment methodology is expected to provide socio-demographic profiles consistent with the adult population based on PATH³ study data for each of the study cohorts. In compliance with CTP's guidance,⁴ regarding intended use and risk assessment in vulnerable populations, the study will oversample the young adult population, specifically people who fall between legal age for tobacco use (by state) and 24 years of age. Additionally, the study will oversample cigarette smokers with intention to quit as assessed by the Motivation to Stop Scale (MTSS).⁵ More information on recruitment of study cohorts is available in the ZYN[®] Likelihood of Use Study protocol (the Study Protocol).⁶

After recruitment, participants in the ZYN[®] Likelihood of Use Study will access a 15-20 minute survey where they are asked to self-report current TNP use. Cognitive interviews informed the survey design to ensure that the survey materials were appropriate and sufficiently clear to respondents. More information about the cognitive interviews can be found in the Study Protocol,⁶ while more information on the study survey is available in the ZYN[®] Likelihood of Use Study survey.⁷

6.2 Study Cohorts

The study population consists of the U.S. adult population of legal age for TNP use. To meet the objectives of the ZYN[®] Likelihood of Use Study, the study will include respondents from the following cohorts described in [Table 1](#). Cohorts of interest will be defined based on self-reported TNP use. The definition of TNP use, and the product types constituting TNP for this study, were adapted from the PATH study.³ The PATH study suggests a definition for lifetime cigarette use, which is having smoked 100+ cigarettes in a lifetime. For all other TNP, usage is based on recollection of ever using any particular TNP fairly regularly.³ Current use is based on now using the product every day or some days.³ Cohorts with and without intention to quit cigarettes will be defined using the MTSS,⁵ which is described in more detail in [Section 6.5.1](#).

6.2.1 Subject Selection: Inclusion Criteria

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

- Minimum legal age per local requirements.
- Able to read and speak English.
- Currently a resident of the United States.
- Individuals who provide electronic informed consent.

6.2.2 Subject Selection: Exclusion Criteria

Respondents who meet any of the following criteria will be excluded:

- Respond 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), since used for balancing cohorts.

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- Unwilling or unable to provide informed consent.
- Individual employed in any of the following fields or professions: market research, marketing, advertising, employee of a TNP manufacturer, or physician.
- Individuals who have taken part in a consumer research study on tobacco in the past 2 weeks, or respond as “Don’t know” or “Decline to answer” when asked.

Table 1. Study Cohorts.

<p>Never tobacco users</p>	<ul style="list-style-type: none"> • Have NEVER used the following products: <ul style="list-style-type: none"> ▪ Cigarettes ▪ E-cigarettes ▪ Cigars, cigarillos, filtered cigars ▪ Pipe filled with tobacco ▪ Nicotine pouches ▪ Hookah or water pipe filled with tobacco ▪ Smokeless tobacco (snus pouches, moist snuff, dip, or chewing tobacco) • OR ALL of the following: <ul style="list-style-type: none"> ▪ Smoked fewer than 100 cigarettes during their lifetime AND now do not smoke every day or some days AND ▪ For each of the following products, have never been a regular user AND now do not use the product every day or some days: <ul style="list-style-type: none"> - E-cigarettes - Cigars, cigarillos, filtered cigars - Pipe filled with tobacco - Nicotine pouches - Hookah or water pipe filled with tobacco - Smokeless tobacco (snus pouches, moist snuff, dip, or chewing tobacco)
<p>Former tobacco users</p>	<ul style="list-style-type: none"> • Have smoked 100 or more cigarettes during lifetime AND currently do not smoke cigarettes every day or some days <p>AND/OR</p> <ul style="list-style-type: none"> • For any of the following products, have been a regular user BUT now do not use every day or some days:

(b) (4)

	<ul style="list-style-type: none"> ▪ E-cigarettes ▪ Cigars, cigarillos, filtered cigars ▪ Pipe filled with tobacco ▪ Nicotine pouches ▪ Hookah or water pipe filled with tobacco ▪ Smokeless tobacco (snus pouches, moist snuff, dip, or chewing tobacco)
Current cigarette smokers <u>with</u> intention to quit	<ul style="list-style-type: none"> • Have smoked 100 or more cigarettes during lifetime AND • Currently smoke cigarettes every day or some days AND • Have intention to quit (score 5-7 on the Motivation to Stop Scale [MTSS])⁵
Current cigarette smokers <u>without</u> intention to quit	<ul style="list-style-type: none"> • Have smoked 100 or more cigarettes during lifetime AND • Currently smoke cigarettes every day or some days AND • Have no intention to quit (score of 1-4 on MTSS⁵)
Current tobacco users (excluding cigarettes)	<ul style="list-style-type: none"> • For any of the following products, have been a regular user AND now use the product every day or some days: <ul style="list-style-type: none"> ▪ E-cigarettes ▪ Cigars, cigarillos, filtered cigars ▪ Pipe filled with tobacco ▪ Nicotine pouches ▪ Hookah or water pipe filled with tobacco ▪ Smokeless tobacco (snus pouches, moist snuff, dip, or chewing tobacco) <p>AND</p> <ul style="list-style-type: none"> • Have smoked cigarettes during lifetime (fewer than 100 <u>or</u> 100 or more in lifetime) AND currently do not smoke cigarettes every day or some days <p>OR have never smoked</p>

6.3 Precision Analysis

A precision analysis was used to inform the sample sizes for all cohorts of interest, with the purpose of ensuring that study samples allow for robust evaluation of the objectives. The precision analysis was performed under the following assumptions: a confidence interval of 95% ($\alpha=.05$), a standard

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deviation of 3.74,^b a small interval half-width, and a probability of achieving the desired precision of .99.

6.4 Study Sample Size

The precision analysis suggested a sample size of (b) (4) per cohort would be appropriate. In total, the planned study sample is (b) (4), with (b) (4) respondents in each cohort. Table 2 presents the sample size for each cohort, along with the percent of sample per cohort, and the estimated percent of the adult population that each cohort represents based on PATH estimates.³ In compliance with the CTP's guidance regarding intended use and risk assessment in vulnerable populations, this study will oversample the young adult population among never users and current cigarette smokers, specifically people who fall between the legal age for tobacco use in their states, to age 24.⁴

Table 2. Sample sizes for the ZYN® Likelihood of Use Study.

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^b The standard deviation used in these power calculations are taken from data provided by Swedish Match, "A market research report (January 2017)" which uses the Juster Scale to measure purchase intentions for moist snuff. The standard deviation is an average of the 3 standard deviations taken from Question #9, 13, and 17.

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6.5 Variables of Relevance to the Study

6.5.1 Outcomes

Pre-exposure

Pre-exposure outcomes that will be used to evaluate the primary objectives are as follows:

Current intention to buy TNP will be assessed with the 11-point Juster Scale, one survey item per TNP type. The Juster Scale is a probability scale that can be used to produce estimates of the average probability that a population will perform a certain behavior by a future time.⁸ As the Juster Scale measures probability, the mean response predicts the proportion of the population that will perform the behavior.⁸ Research has shown that the Juster Scale is effective in predicting consumers' future purchasing behaviors.⁹

Current use of TNP will be assessed by measuring present frequency of use for each TNP, utilizing one survey item per TNP type. This approach mimics methodology measuring current TNP use employed in PATH.³ Response options for frequency of use include "Every day," "Some days," "Not at all," "Don't know" and "Decline to answer."

Current intention to quit TNP will be measured by the one-item validated instrument, the MTSS.⁵ 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 use the MTSS both for assessing intention to quit cigarettes and for other TNPs. Consistent with published research using the MTSS, we will report the mean MTSS score.¹⁰

Pre-exposure outcomes that will be used to evaluate the secondary objectives are as follows:

Pre-exposure perceptions of absolute health risk of non-usage and smoking will be assessed using one item (5-point Likert scale; 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 modified from the risk perception scale in HINTS.¹¹ The 5-point Likert scale used in HINTS had response options where 1= Much less harmful to 5= Much more harmful; we changed the response options to fit with the structure of the question in the survey. Additionally, this measure achieved saturation during cognitive interviewing. Saturation is defined at 80% or more of the respondents being able to verbalize a logical thought process when answering the question that fit with the intent of the question.

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Post-exposure to ZYN[®]

Outcomes captured post-exposure to ZYN[®] that will be used to evaluate the primary objectives are as follows:

Future intention to buy ZYN[®] will be assessed post-exposure to the ZYN[®] description and packaging label via the 11-point Juster Scale. The Juster Scale is explained in more detail under “Current intention to buy TNP” above.

Future intention to use TNP will be assessed post-exposure to the ZYN[®] description and packaging label using a custom, single-item 4-point ordinal scale for each TNP currently used. Response options for the item will include “Quit completely,” “Cut back use,” “Use the same amount” and “Use more”; “Don’t know” and “Decline to answer” will be available as answer options outside of the scale. Cognitive interviewing demonstrated that saturation was achieved for this measure.

Future intention to quit TNP will be measured by the one-item validated instrument, the MTSS.⁵ The MTSS is explained in more detail under “Current intention to quit TNP” above.

Appeal of various ZYN[®] brand and product attributes will be assessed using one item for each brand and product attribute. Specific attributes being investigated include the overall ZYN[®] product, ZYN[®] packaging, ZYN[®] pouches (i.e. the product itself), ZYN[®] child-safety lid, and ZYN[®] variety of flavors. Response options include “Not at all appealing,” “Slightly appealing,” “Moderately appealing,” “Very appealing” and “Extremely appealing”; “Don’t know” and “Decline to answer” will be available as answer options outside of the scale.

Post-exposure outcomes that will be used to evaluate the secondary objectives are as follows:

Perceptions of absolute health risk of the daily use of only ZYN[®] and no other TNP will be assessed using one item (5-point Likert scale; 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 modified from the risk perception scale in HINTS.¹¹ The 5-point Likert scale used in HINTS had response options where 1= much less harmful to 5= much more harmful; we changed the response options to fit with the structure of the question in the survey. Additionally, this measure achieved saturation during cognitive interviewing.

Perceptions of relative health risk will be assessed using one item (5-point Likert scale; 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). In this battery, respondents will evaluate ZYN[®] use against several other risk exposures. The risk exposures to be assessed for each health condition include use of ZYN[®] versus: the daily use of other TNP, aids to help stop smoking, never having used any TNPs, and quitting all

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(b) (4)

TNP relative to quitting all TNP except for ZYN®. This scale was modified from the risk perception scale used in HINTS.¹¹ The 5-point Likert scale used in HINTS had response options where 1= Much less harmful to 5= Much more harmful; we changed the response options to fit with the structure of the question in the survey. Additionally, this measure achieved saturation during cognitive interviewing.

Summaries of the outcomes for primary and secondary objectives, and comprehension check including measurement domain, subcategories, measurement details, and metrics, are presented in [Table 3](#) to [Table 4](#), [Table 5](#) to [Table 6](#), and [Table 7](#), respectively.

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Table 3. Outcomes Table for Primary Objective 1 – Impacts of ZYN® on Perceptions and Intentions Related to the use of TNP.

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Table 5. Outcomes Table for Secondary Objective 1 – Perceptions of Absolute Risk.

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Table 6. Outcomes Table for Secondary Objective 2 – Perceptions of Relative Risk

(b) (4)

(b) (4)

(b) (4)

Measurement Domain	Subcategory	Measurement Method	Measurement Details
	Serious health problems		much higher chance." "Don't know" and "Decline to answer" are also available as response options.
Relative risk attributed to using ZYN® alone after quitting all other TNPs vs. quitting all TNPs and using nothing	Adult tooth loss	One item for each health condition (4 health conditions total) will assess the relative risk of certain health conditions associated with quitting all TNPs except for the daily use of ZYN® and quitting all TNPs and using nothing	Relative risk perception of a person suffering from each health condition when never having used any TNP as compared with using ZYN® only will be assessed with "A much lower chance," "A lower chance," "The same chance," "A higher chance" and "A much higher chance." "Don't know" and "Decline to answer" are also available as response options.
	Gum disease		
	Mouth cancer		
	Serious health problems		
Relative risk attributed to using ZYN® vs. never having used any TNP	Adult tooth loss	One item for each health condition (4 health conditions total) will assess the relative risk of certain health conditions associated with ZYN® alone as opposed to never having used any TNP	Relative risk perception of a person suffering from each health condition when never having used any TNP as compared with using ZYN® only will be assessed with "A much lower chance," "A lower chance," "The same chance," "A higher chance" and "A much higher chance." "Don't know" and "Decline to answer" are also available as response options.
	Gum disease		
	Mouth cancer		
	Serious health problems		

6.5.2 Additional Variables of Interest

Socio-demographic Variables

State of residence, used to derive U.S. census region, will be assessed using a single item asking the respondent what state they spend most days of the year in. State of residence will be categorized into the four U.S. census geographic regions to summarize data collection results: Northeast, South, Midwest, and West.

Age of the respondent will be assessed using a single item asking the respondent how many years old they are. Age of respondent will be categorized for reporting using the following age groups: 18-20, 21-24, 25-34, 35-44, 45-54, and 55+ years old.

Gender will be assessed using a single item asking the respondent if they are male or female.

Racial or ethnic background will be assessed using a single item asking the respondent which best describes their racial/ethnic background. Response options include: 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 will be assessed using a single item asking the respondent which response corresponds to the highest level of education they have attained. Response options include: 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 a post-graduate degree (e.g., MBA, PhD, JD, etc.).

Marital Status will be assessed using a single item asking the respondent their marital status. Response options include: Now married, widowed, divorced, separated, never married, and decline to answer.

Pregnancy Status will be assessed using a single item asking female respondents their pregnancy status. Response options include: I am currently pregnant, I am intending on getting pregnant in the next 6 months, none of the above, don't know, and decline to answer.

Number of adults who live in the household will be 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 will be categorized for reporting as 1, 2, 3, 4, or 5+.

Number of children who live in the household will be assessed using a single item asking the respondent for the number of individuals living in the household who are under 18 years old. Decline

(b) (4)

(b) (4)

to answer is also available as a response option. Number of children in the household will be categorized for reporting as 1, 2, 3, 4, or 5+.

Household income in the last 12 months will be assessed using a single item asking respondents which category best describes their total household income in the last 12 months. Response options include: 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.

Comprehension Check

Comprehension of ZYN[®] description and packaging label will be assessed by using one item measuring comprehension of the various pieces of information presented in the ZYN[®] description and packaging label. The multiple-choice response options include: ZYN[®] contains nicotine, the package label includes a warning that nicotine is an addictive chemical, ZYN[®] comes in the form of chewing gum, ZYN[®] comes in a total of three flavors, ZYN[®] comes in both 3 mg of nicotine and 6 mg of nicotine varieties, don't know, and decline to answer.

7. STATISTICAL ANALYSIS

7.1 Presentation of Analysis Results

For preliminary descriptive analysis, numerical data will be presented by the total N-size, missing values (if applicable), mean, standard deviation (SD), median, minimum, and maximum. Continuous data, if reported as such, will be displayed to 2 decimal places. Otherwise, continuous data will be grouped into ranges and summarized by frequencies and percentages. Categorical data will be presented using frequencies (counts) and percentages; the number of missing values will also be presented (if applicable). Multiple response data will be presented as a distribution of single entries or according to pre-specified top-2 box and/or bottom-2 box groupings. Percentages will be displayed to 1 decimal place and counts with zero decimal places.

7.2 Study Analysis

All analyses performed for the ZYN[®] Patterns of Use Study will be descriptive in nature.

Descriptive statistics used to understand the distribution of outcomes and socio-demographic variables (see [Section 6.5.1](#) and [Section 6.5.2](#)) will be calculated prior to any recoding or aggregation that might be utilized for presentation of results. Respondents with values for variables that are illogical or deemed unreliable, as determined by the underlying distribution and individual examination, will be

considered for removal prior to performing the main analyses. (See [Section 8.2](#) and [Section 8.3](#) for details regarding this process). Numeric variables will be described using total sample size, number of missing observations (if applicable), means, standard deviations, medians, minimums, and maximums. Categorical variables will be described using frequencies, percentages, and the number of missing observations (if applicable).

Unless otherwise specified in the table shells ([Section 10](#)), descriptive statistics reported for the main analyses will include the number of non-missing observations, means, standard deviations, and 95% confidence intervals (CIs) for numeric variables. For categorical variables they will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents relevant for each outcome.

The study team will format and properly label the data sets (including all responses from respondents and the date that the survey was completed) using SAS® software (Statistical Analysis System, version 9.3)¹² so they are suitable for analysis. The data sets will contain a subject ID number and will not contain any information that could be used to identify individual respondents.

7.3 Socio-demographics and Comprehension Check

Descriptive statistics will be reported for all socio-demographic variables, as well as the comprehension check outlined in [Section 6.5.2](#). Specifically, U.S. census region, age of respondent, gender, racial or ethnic background, highest grade or level of school completed, marital status, pregnancy status, number of adults who live in the household, number of children who live in the household, household income in the last 12 months, and comprehension of the ZYN® description and packaging label will be reported for all cohorts. [Table 12](#) presents a table shell reflecting how descriptive statistics for socio-demographic and comprehension check variables will be reported.

7.4 Primary Objectives

Descriptive statistics for accomplishing primary objectives will be reported for current intention to buy TNP, future intention to buy ZYN®, current use of TNP, future intention to use TNP, current and future intention to quit TNP, and appeal of ZYN® brand and product attributes. Descriptive statistics will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category for categorical variables. [Table 8](#) and [Table 9](#) below provide summaries of the analyses that will be used to accomplish the primary objectives, including the objective, outcomes, cohorts, and the statistical analysis. [Table 13](#) to [Table 18](#) present table shells for reporting the results.

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7.5 Secondary Objectives

Descriptive statistics for accomplishing secondary objectives will be reported for absolute risk outcomes, and relative risk outcomes. Descriptive statistics will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category for categorical variables. [Table 10](#) and [Table 11](#) below provide summaries of the analyses that will be used to accomplish the secondary objectives, including the objective, outcomes, cohorts, and the statistical analysis. [Table 19](#) to [Table 24](#) present tables shells for reporting the results.

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STATISTICAL ANALYSIS PLAN

ZYN[®] Likelihood of Use

Swedish Match North America

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Table 7. Analysis Table for Primary Objective 1 – Impacts of ZYN[®] on Perceptions and Intentions Related to the use of TNP.

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STATISTICAL ANALYSIS PLAN
ZYN® Likelihood of Use
Swedish Match North America

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Table 9. Analysis Table for Secondary Objective 1 – Percentions of Absolute Risk.

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STATISTICAL ANALYSIS PLAN
ZYN® Likelihood of Use
Swedish Match North America
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Table 10. Analysis Table for Secondary Objective 2 – Perceptions of Relative Risk.

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ZYN® Likelihood of Use

Swedish Match North America

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STATISTICAL ANALYSIS PLAN
ZYN® Likelihood of Use
Swedish Match North America

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8. STATISTICAL AND ANALYTICAL ISSUES

8.1 Data Capture and Management

8.1.1 Data Capture

The web-based survey will be 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 will be reviewed by a separate team within (b) (4) fielding operations group from the perspective of the respondent (i.e. the link is reviewed online and not within the (b) (4) software).

The data collected for this study will be monitored for adherence with the Study Protocol.⁶ All data will be collected using a programmed web Survey.⁷ Prior to initiating the study, appropriate edit programming will be conducted to assure the final dataset requires minimal cleaning of invalid responses. These programming procedures for the web-based survey data entry tool will include response ranges, consistency checks, skip patterns, and other special edit procedures where applicable. At every step of data processing, results or creating grouping variables will be cross checked by (b) (4) operations team members who independently replicate the results and/or verify that the data have been handled appropriately and accurately. Any inconsistencies identified during this process are corrected before data are provided to (b) (4) analytical team to begin study analysis.

8.1.2 Data Management and Analysis QC Process

- Until the approval of the ZYN[®] Likelihood of Use SAP by SMNA, the data will remain blinded and locked to those involved in SAP development.
- Once data are unlocked, the analytical team will perform 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 will be checked.
 - Completion of the survey will be verified, and any respondent who did not complete the full survey will be removed from analysis.
 - It will be verified that respondents satisfied the inclusion and exclusion criteria.
 - The actual quota frequencies for each study cohort in the data set will be compared against the quota frequencies specified in the Study Protocol. Any discrepancies will be documented in the final report.
- All variable coding will follow 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).

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- All statistical analyses and results output will be checked by another researcher on the analytical team for quality control. These checks will include:
 - Correct coding of variables
 - Correct use of statistical tests as specified in the analysis section
 - Correct export of results from SAS® output to Excel tables

8.2 Handling of Missing Data

The structure of the questionnaire does not have “true” missing data. The online survey does not allow respondents to proceed without receiving an answer to the present question. No partially completed surveys will be included in the final data set, or analyses. Data points are 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 will be kept as is and will be reported descriptively (percentages and counts). The questionnaire was designed (and tested with cognitive interviews) so that instructions are as easy to understand and clear as possible to help avoid missing data.

The rationale and utilization of “Don’t know” and “Decline to answer” response options are as follows:

- In this study, a “Decline to answer” response option without a “Don’t Know” option will be provided for any question where there is personally sensitive information, but the answer would be known to the respondent (e.g., age, gender, etc.).
- “Don’t know” and “Decline to answer” options will be provided for all other questions.

8.3 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 do not compromise the integrity of the data, measures are taken to identify them in a systematic and objective way prior to actual analyses. No respondent will be removed from the full study analyses. However, should the process below identify outliers, sensitivity analyses will be conducted without these respondents to determine whether results differ from the full sample analyses. The process will seek to identify the following respondent types:
 - Respondents who lack variability in their responses to a battery of questions (“straight liners”) will be identified using standard deviations customized for each outcome found in the survey. Respondents whose responses have a standard deviation of zero or greater than four times the overall standard deviation will be flagged and examined individually.
 - Similarly, respondents who demonstrate a discernable pattern in their answers inconsistent with any coherent understanding of the question (e.g., selecting 1, 2, 3, 4, 5, 1, 2, 3, 4, 5, 1... etc.) will also be flagged and examined individually.

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- Respondents who are straight lining or giving patterned responses consistently throughout the survey (i.e., across multiple sections of the survey) will be individually scrutinized.
- Respondents found to lack credibility will be identified, handled consistently and transparently, and documented in the final report. This said, the a priori assumption is that all data reported is true, and accurate and preliminary outliers will be identified based on the underlying distribution of the data, and through descriptive analysis.
- Data from non-credible respondents will be flagged in the data file. Additionally, the number of respondents flagged and the rationale for their identification as outliers will be reported in the final report.
- Sensitivity analyses will be conducted for every outcome with the outliers removed. The results of the sensitivity analyses will be reported as to whether the exclusion of the outliers changed the descriptive results in a substantive way.

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9. REFERENCES

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10. TABLE SHELLS

Table 11. Socio-demographic and Comprehension Check Variables for all study participants.

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STATISTICAL ANALYSIS PLAN

ZYN® Likelihood of Use

Swedish Match North America

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Table 12. Table Shell for Primary Objective 1 – Likelihood to Initiate or Reinitiate TNP.

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Table 13. Table Shell for Primary Objective 1 – Current Use of TNP among TNP Users.

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Table 14. Table Shell for Primary Objective 1 – Future Intention to Buy ZYN® among TNP Users.

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Table 15. Table Shell for Primary Objective 1 – Future Intention to Use Current TNP after Exposure to ZYN[®].

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ZYN® Likelihood of Use

Swedish Match North America

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Table 16. Table Shell for Primary Objective 1 – Current Intention to Quit TNP and Future Intention to Quit TNP.

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Table 17. Table Shell for Primary Objective 2 – Appeal of ZYN® Brand and Product Attributes.

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Table 18. Table Shell for Secondary Objective 1 – Perceptions of Absolute Risk to a Person who Smokes Cigarettes Every Day but Uses no Other Tobacco Products.

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ZYN® Likelihood of Use

Swedish Match North America

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Table 19. Table Shell for Secondary Objective 1 – Perceptions of Absolute Risk Associated With Never Having Used any TNPs.

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Table 20. Table Shell for Secondary Objective 1 – Perceptions of Absolute Risk Associated Using Only ZYN[®] Daily.

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ZYN® Likelihood of Use
Swedish Match North America
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Table 21. Table Shell for Secondary Objective 2 – Perceptions of Relative Risk of Adult Tooth Loss.

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Table 23. Table Shell for Secondary Objective 2 – Perceptions of Relative Risk of Mouth Cancer.

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Table 24. Table Shell for Secondary Objective 2 – Perceptions of Relative Risk of Serious Health Problems.

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INVESTIGATOR SIGNATURE

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Investigator (Main Author):

Name (typed or printed):

(b) (4), (b) (6)

Company:

(b) (4)

Signature:

(b) (6)

Date: 1 June 2018

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to SMNA; a protocol amendment will not be required.

SPONSOR SIGNATURE

Sponsor:

Name (typed or printed):

(b) (4), (b) (6)

Company:

Swedish Match North America

Signature:

(b) (6)

Date: 31 May 2018

(Day Month Year)

(b) (4)

STATISTICAL ANALYSIS PLAN
ZYN® Likelihood of Use
Swedish Match North America

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Swedish Match.

Swedish Match North America, Inc.

Statistical Analysis Plan

ZYN® Likelihood of Use Study

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SIGNATURE PAGE

I agree to the terms of this ZYN® Likelihood of Use SAP.

Name (typed or printed):

(b) (4), (b) (6)

Institution:

(b) (4)

Signature:

(b) (6)

Date: 8 June 2018

(Day Month Year)

Name (typed or printed):

(b) (4), (b) (6)

Institution:

Swedish Match North America

Signature

(b) (6)

Date: 8 June 2018

(Day Month Year)

SIGNATURE PAGE

I approve of this ZYN® *Likelihood of Use* final report.

Name (typed or
printed):

(b) (4), (b) (6)

Institution:

(b) (4)

Signature:

(b) (6)

Date: 6 August 2018

(Day Month Year)

Name (typed or
printed):

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Institution:

Swedish Match North America

Signature:

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