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Center for Tobacco Products

Swedish Match USA Modified Risk Tobacco Product Application for ZYN

Presentation Will Begin Shortly

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Swedish Match USA Modified Risk Tobacco Product Application for ZYN

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Agenda

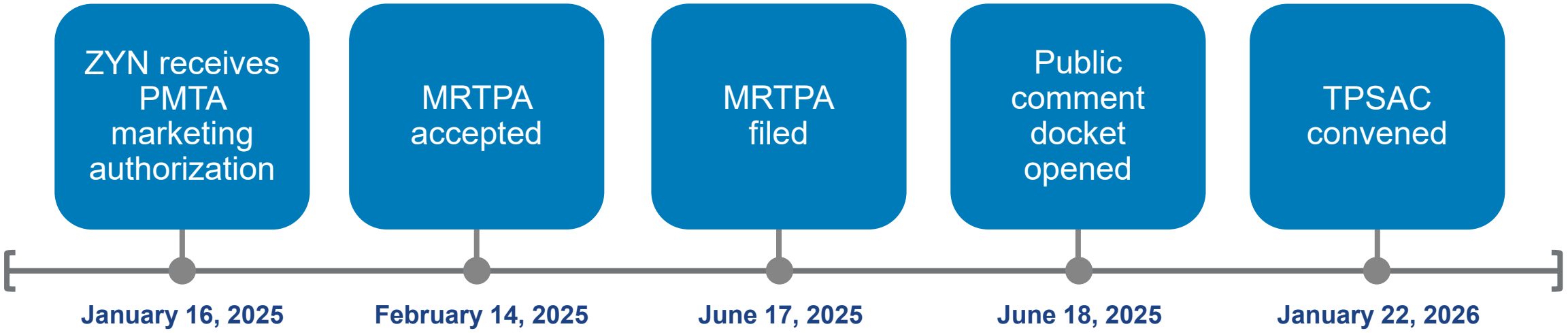
- Summary of Swedish Match USA modified risk tobacco product application (MRTPA) under review
- Lines of scientific evidence
- Discussion topics for the committee

ZYN

- 20 products
- Product format: 400 mg sealed pouches
- Nicotine source: tobacco-derived nicotine
- Nicotine formulation: nicotine salt
- Nicotine strength: 3mg or 6mg
- Flavors: variety
- Tobacco leaf content: no whole, cut, or ground tobacco
- The applicant states the intended use is as follows: the product is held between the lip and the gum for a period of use and then discarded

Swedish Match USA MRTPA Submission

The applicant is seeking a risk modification order under 911(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for twenty ZYN nicotine pouch products



Proposed Modified Risk Claim

“Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis”

Requirements for a 911(g)(1) Risk Modification Order

For these orders, applicants must demonstrate that such product, as it is actually used by consumers, will:

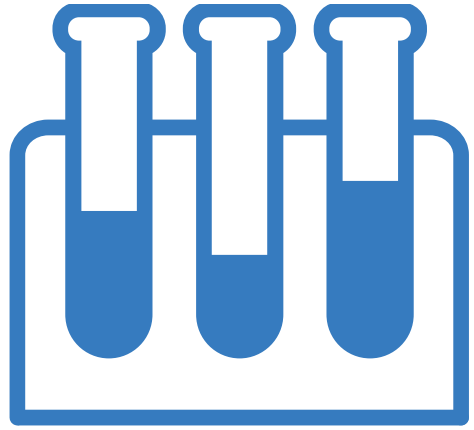
- Significantly reduce harm and the risk of tobacco-related disease to individuals who use tobacco products
- Benefit the health of the population as a whole, taking into account both persons who use tobacco products and persons who do not currently use tobacco products

The advertising and labeling of the proposed MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all the tobacco diseases and health-related conditions associated with the use of tobacco products (section 911(h)(1))

Relative Health Risks to Individuals

Harmful and Potentially Harmful Constituents

- Harmful and Potentially Harmful Constituents (HPHCs) are chemicals or chemical compounds in tobacco products or tobacco smoke or emission that cause or could cause harm to people who use tobacco products and people who do not use tobacco products.
- Testing results showed that levels of 36 of the 42 HPHCs reported for ZYN are below the level of quantification (2025 PMTA Decision Summary).
- Among the HPHCs that were quantifiable in ZYN, none were at levels expected to pose a risk to health.
- Levels of nearly all HPHCs reported were lower in ZYN than General Snus.
- In a direct comparison between ZYN and mainstream combusted cigarette smoke, all HPHCs, besides nicotine, are lower in ZYN than in combusted cigarette smoke.

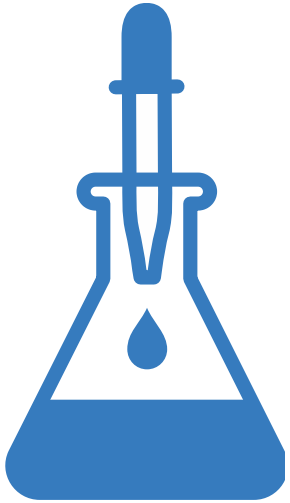


Biomarker Study SM22-03: Methods

- Biomarkers of exposure (BOE): assess the level of human exposure to chemicals (e.g., HPHCs) as a result of using tobacco products.
- Biomarkers of potential harm (BOPH): measurements of biological changes in humans due to an exposure, that may indicate a change in long-term disease risk.
- Applicant submitted a non-randomized, cross-sectional, multi-center study conducted in Sweden from January 12, 2023 to March 15, 2023.
- A total of 198 healthy adult volunteers from a clinical trial database, media advertisements and marketing campaigns eligible if one of the following:
  - exclusive daily use of one brand of Swedish Match nicotine pouch products (3-16 mg nicotine/pouch)
  - exclusive daily use of Swedish tobacco-based snus (4-20 mg nicotine/pouch)
  - exclusive daily use of combusted cigarettes
  - <100 lifetime tobacco uses and no use in the past year
- Participants in the tobacco use groups used their product of choice exclusively as desired over 14 days with blood and urine samples collected at Days 1 and 14.

Biomarker Study SM22-03: Results and Discussion

- Biomarker profiles of adults who use nicotine pouches were frequently similar to adults who do not use tobacco and consistently lower than those who smoke combusted cigarettes:
  - Significantly lower levels of tobacco-specific nitrosamines (TSNAs), NNAL and NNN, compared with adults who use snus and adults who use combusted cigarettes.
  - Generally lower inflammation and oxidative stress biomarkers compared to adults who use combusted cigarettes and often comparable to adults who do not use tobacco.
- Similar nicotine-related biomarker levels to adults who use snus but higher than adults who use combusted cigarettes.
- Limitations of biomarker study
  - Cross-sectional design
  - No adjustments for sociodemographic or behavioral variables
  - Participants were asked to use only one product exclusively for 14 days
  - Not product-specific though 65% used ZYN
    - Some participants using ZYN used flavors and nicotine concentrations different from those in the FDA authorized products



Relevance of Swedish Snus Epidemiological Studies to ZYN

- Nicotine pouches are a product category that is relatively newer than other well-established tobacco product categories, and there are currently no long-term health data specific to these products.
- The applicant states published literature on the long-term health effects of Swedish snus are applicable to ZYN. Similarities include:
  - Product characteristics
    - Appearance
    - Both manufactured by applicant
    - Similar flavors
    - Comparable nicotine content, pH, route of exposure
  - Use patterns
    - Placed in oral cavity
    - Frequency, duration, amount of use
  - Consumer characteristics
    - Many people who ZYN previously used moist snuff

Swedish Snus Epidemiological Studies: Mouth Cancer

- Pooled analysis of nine Swedish cohort studies (Araghi et al., 2021):
  - Ever vs never snus use was not clearly associated with oral cancer (aHR 0.90; 95% CI: 0.74–1.09).
  - Among people who never smoked (HR 0.87; 95% CI: 0.57–1.32).

- By comparison, combusted cigarette smoking is associated with about 5-11 times the risk of oral cancer as never smoking (CPS II, 1982-1988; unpublished estimates provided by American Cancer Society).

Swedish Snus Epidemiological Studies: Lung Cancer

- Cohort of 279,897 never-smoking Swedish construction workers (Luo et al., 2007):
  - Relative risk of 0.8 (95% CI: 0.5–1.3) for lung cancer for snus use vs. no use.

- People who smoke combusted cigarettes have about 25 times the risk of dying from lung cancer as those who never smoked combusted cigarettes (Thun et al., 2013).

Swedish Snus Epidemiological Studies: Heart Disease

- Meta-analysis (Lee et al., 2022):
  - Among people who never smoked, current snus use not associated with risk of ischemic heart disease or acute myocardial infarction.
- Pooled analysis (Byhamre et al, 2021):
  - Among people who never smoked, current snus use was associated with the risk of dying from cardiovascular disease (aHR=1.27, 95% CI:1.15-1.41).
- Combusted cigarette smoking increased risk of dying from cardiovascular disease (CVD) by about 2.5- to 3 times that of adults who never smoked combusted cigarettes (Thun et al., 2013).
- Effects of nicotine would not be expected to be different for snus compared to other nicotine-containing products. Combusted cigarette smoke, however, has other cardiovascular toxins not found in snus.

Swedish Snus Epidemiological Studies: Stroke

- Systematic review and meta-analysis (Rostron et al., 2018):
  - Sweden: Among people who never smoked, current snus use not associated with stroke (RR = 1.04; 95% CI: 0.92–1.17).
  - US: Among people who never smoked, smokeless tobacco use associated with stroke (RR = 1.28; 95% CI: 1.01–1.62).
- Combusted cigarette smoking increases risk of dying from stroke by 2 times that of never smoking (Thun et al., 2013).

Swedish Snus Epidemiological Studies: Emphysema and Chronic Bronchitis

- No inhalation of toxicants: association between smokeless tobacco product use and chronic respiratory disease is not expected.
- Combusted cigarette smoking associated with 22-25 times the risk of dying from chronic obstructive pulmonary disease as those who never smoked (Thun et al., 2013).

Summary of Health Effects as Applied to the Proposed Claim

- "Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."
  - Mouth Cancer: Large pooled analyses and cohort studies do not clearly show increased risk for people who use snus, and risk is lower than for people who smoke combusted cigarettes
  - Heart Disease: Meta-analyses and cohort studies find no excess cardiovascular risk in people who never smoked who use snus; risk is lower than smoking.
  - Lung Cancer: Evidence shows no increased risk with snus, whereas smoking increases risk up to 30-fold.
  - Stroke: Swedish studies show no elevated stroke risk from snus; people who smoke have a statistically significant higher risk.
  - Emphysema & Chronic Bronchitis: As non-inhaled products, snus and nicotine pouches are not expected to cause chronic respiratory disease; risk remains minimal compared to smoking.
- As concluded in FDA's prior reviews, the totality of Swedish snus literature indicates that completely switching from combusted cigarettes to snus reduces the risks of these smoking-related diseases.
- ZYN products have similar use patterns, but lower HPHC levels compared to Swedish snus, thus health effects of ZYN are expected to be lower than that of snus use.
- Therefore, completely switching from combusted cigarettes to ZYN is expected to reduce the risks of these smoking-related diseases.

Summary of Relative Health Risks and Proposed Modified Risk Claim

- Product testing: majority of HPHCs are below the level of quantification in ZYN.
- Biomarker study: biomarkers corresponding to HPHCs are lower or below the level of quantification among people who use nicotine pouches as compared to those who use snus or combusted cigarettes.
- No long-term studies of health risk of new products such as nicotine pouches, but long-term studies of Swedish snus use can be considered applicable given the similarities.
  - FDA previously concluded that snus use poses lower risk compared to combusted cigarette smoking for mouth cancer, heart disease, stroke, lung cancer, emphysema, and chronic bronchitis (2019 MRTPA decision summary).
- The evidence suggests the proposed modified risk claim “Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis” is scientifically accurate.

Consumer Understanding and Perceptions

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Three Components of Consumer Understanding

Would the modified risk LLA[1] enable the public to understand…

- what risk reduction or exposure reduction is described?
- that the proposed MRTP does confer health risks or harm and is more harmful than non-use or cessation?
- how to use the proposed MRTP to reduce one's risk or exposure?

[1]labels, labeling, and advertising

Consumer Perceptions and Likelihood of Use Study[1]

1

Main Outcomes

- Intentions to use tobacco products
- Intentions to use ZYN nicotine pouches
- Intentions to quit smoking
- Absolute and relative risk perceptions of ZYN
- Comprehension of label elements exclusive of the claim

2

Design

- Pre-test/post-test
- Non-random assignment to view stimuli with the proposed claim (test condition) or without the proposed claim (control condition)
- Conducted online February-March 2024
- Reviewed by commercial IRB and received exempt determination

3

Sample

- Recruited from aggregated consumer panels
- 3,450 respondents stratified by current and past tobacco use
  - Current combusted cigarette use (n=1,010)
  - Former combusted cigarette use/current other tobacco product use (n=610)
  - Current smokeless tobacco product use (n=610)
  - Non-established tobacco product use ages 21+ (n=610)
  - Non-established tobacco product use ages 21-24 (n=610)

4

Procedure

- Screening
- Assignment to view an advertisement with the claim (test) or without it (control)
- Pre-test
- View assigned advertisement
- Post-test

[1] Full title: Quantitative Study to Assess Perceptions of and Likelihood of Use of ZYN® with Modified Risk Claims Among US Adults

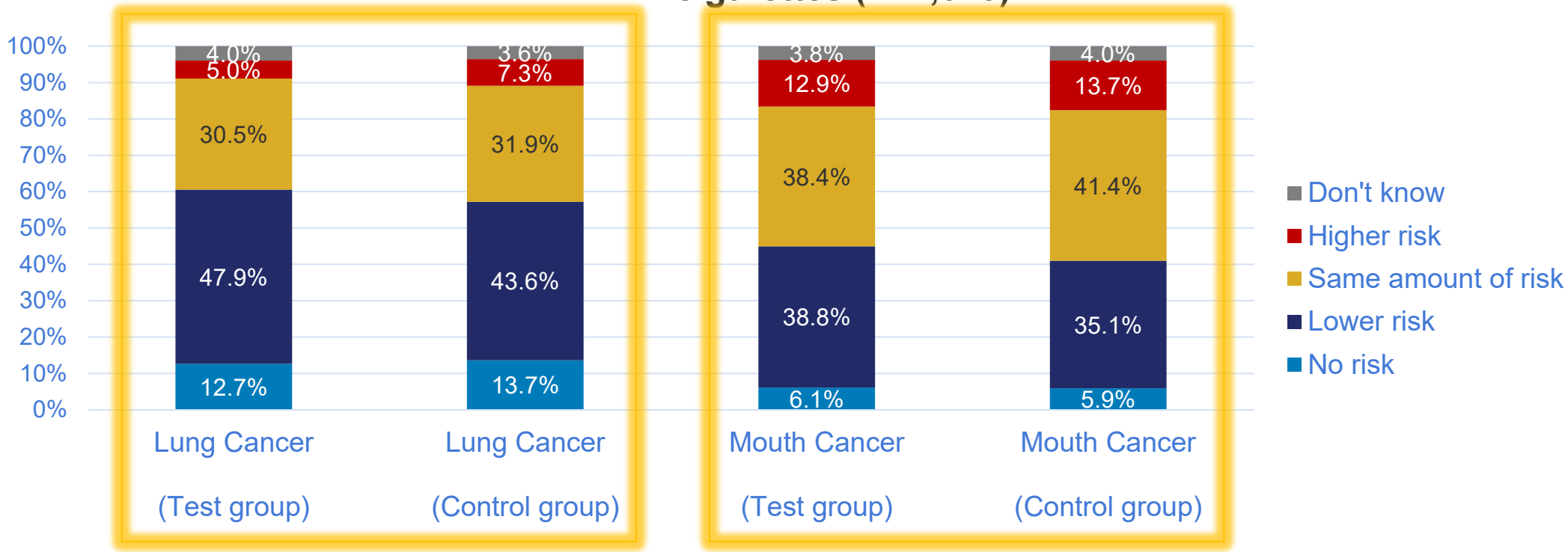
Consumer Perceptions and Likelihood of Use Study Stimuli

With the Claim (Test)

Without the Claim (Control)

Understanding the relative risk of ZYN compared to combusted cigarettes

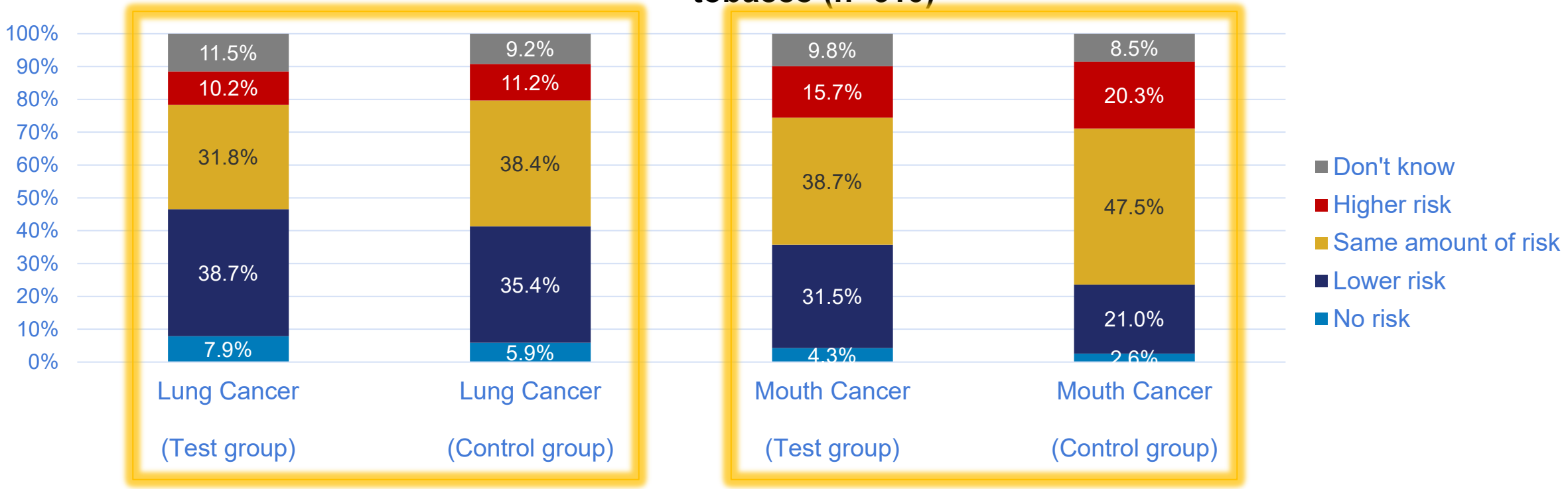
Perceptions of relative lung cancer risk and mouth cancer risk of ZYN compared to combusted cigarettes among adults who use combusted cigarettes (n=1,010)



- These findings align with the broader research suggesting that people tend to overestimate the risks of other tobacco products relative to combusted cigarettes (e.g., Kaufman et al., 2014; Regan, Dube, & Arrazola, 2012; Denlinger-Apte et al., 2021; Vogel et al., 2022; Wackowski, Ray, & Stapleton, 2019; Wackowski & Delnevo, 2016; Popova & Ling, 2013)

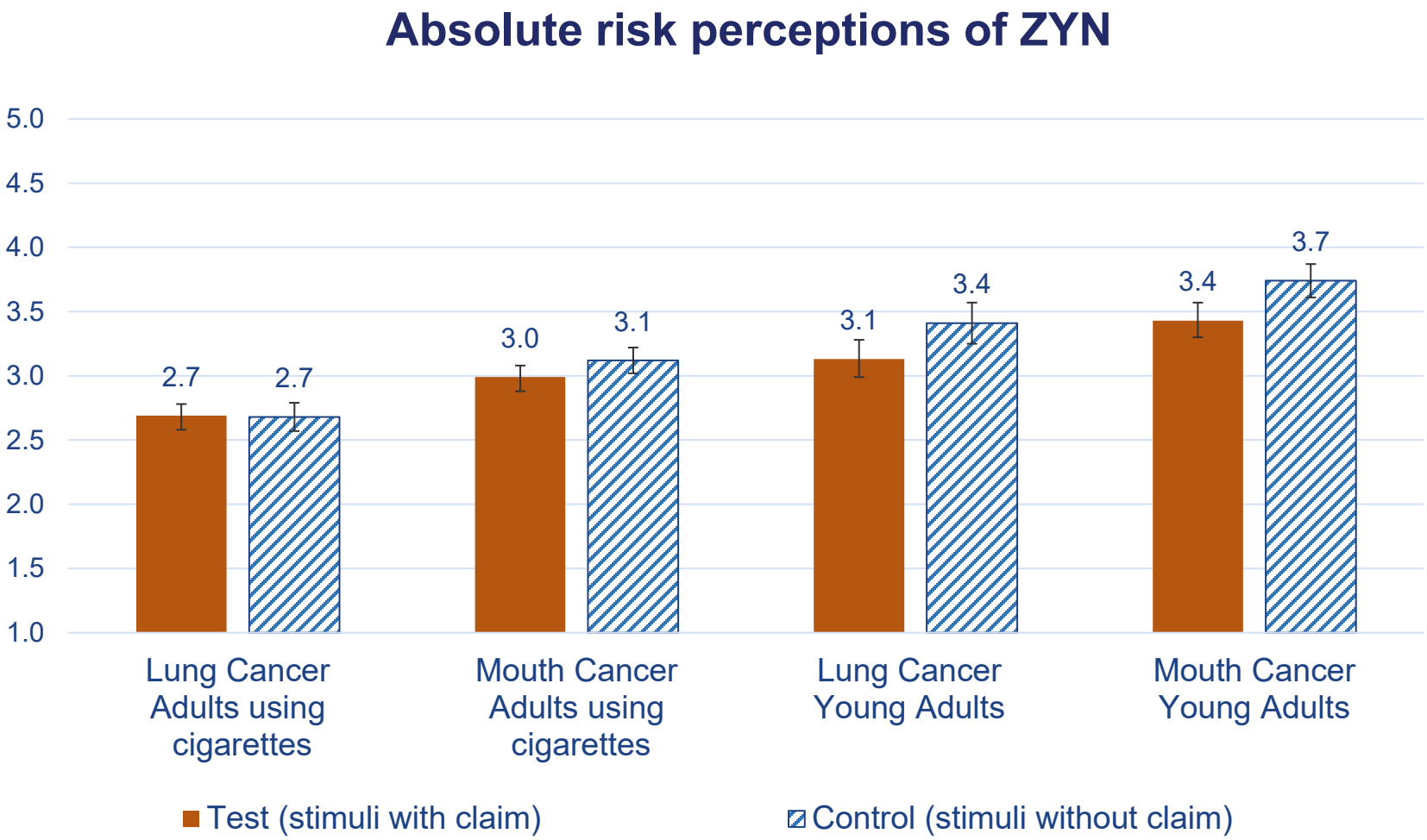
Understanding the relative risk of ZYN compared to combusted cigarettes

Perceptions of relative lung cancer risk and mouth cancer risk of ZYN compared to combusted cigarettes among young adults (ages 21-24) who never regularly used tobacco (n=610)



- These findings align with the broader research suggesting that people tend to overestimate the risks of other tobacco products relative to combusted cigarettes (e.g., Czoli et al., 2017; Morean et al., 2023; Wackowski & Delnevo, 2016)

Understanding that ZYN still confers health risk



Respondents rated absolute risk perceptions of ZYN on a 5-point scale (ranging from 1 = “No Risk” to 5 = “Very High Risk”).

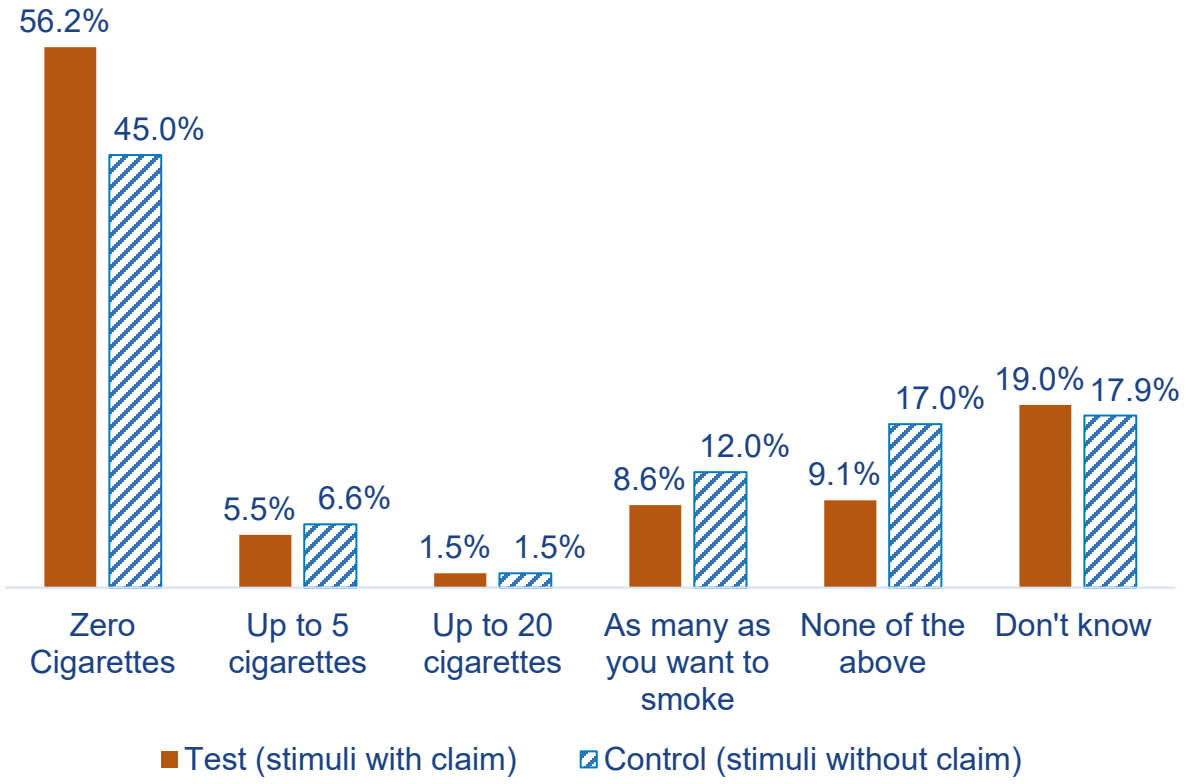
Understanding How to Use the MRTP to Reduce Risk

- The applicant cross-referenced their Perceptions and Behavioral Intentions (PBI) study included in the General Snus MRTPA.
- The proposed claim for ZYN and the authorized claim for General Snus are nearly identical.

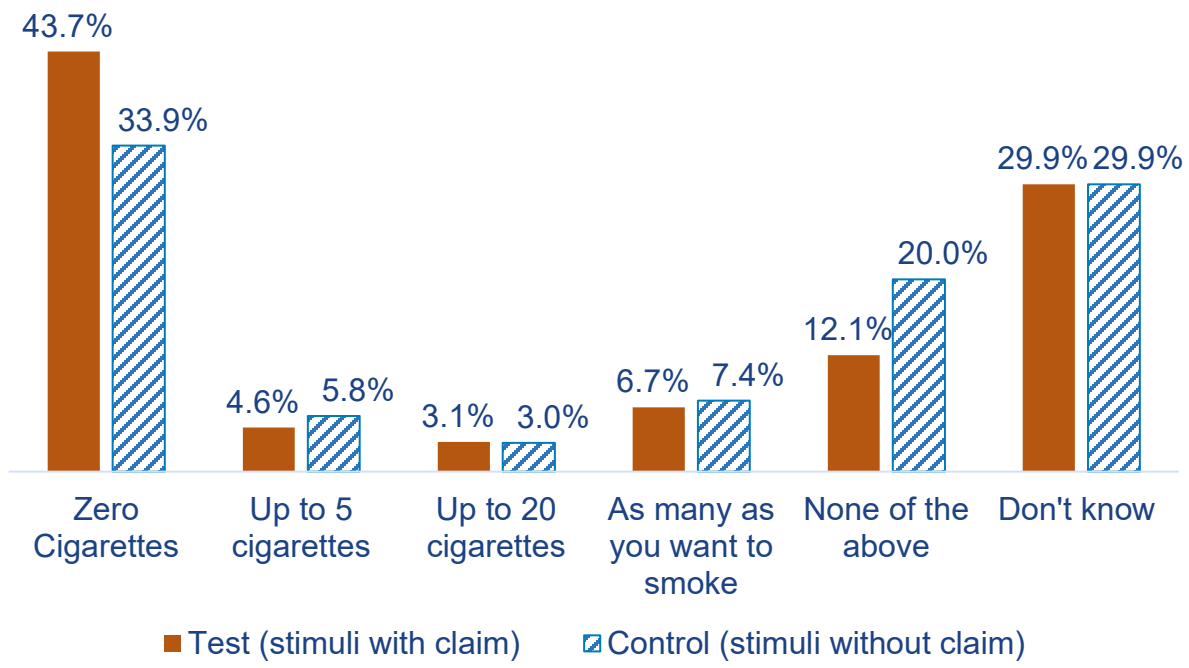
General Snus	ZYN
"Using **General Snus** instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."	"Using **ZYN** instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

Understanding How to Use MRTP (General Snus) to Reduce Risk

Young adults using combusted cigarettes (21-24)



Adults using combusted cigarettes (24+)



Summary: Consumer Understanding and Perceptions

- Consumers correctly understood the risk reduction described in the claim (i.e., ZYN confers lower risk than combusted cigarettes).
- Consumers correctly understood that although conferring lower risk than combusted cigarettes, ZYN still confers health risks.
- Consumers correctly understood how to use a product with the proposed claim to confer lower risk.
- Misunderstanding of the claim was not in the direction of underestimating risks associated with using ZYN; many consumers overestimated risks associated with ZYN regardless of claim exposure.

Likelihood of Use and Impacts to the Population

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Adult Prevalence of Use Without the Proposed Claim: TUS-CPS

Tobacco Use Supplement to the Current Population Survey (2022-2023)

- 0.4% of US adults reported current use of nicotine pouches
- Among adults who reported current nicotine pouch use:
  - 24.8% reported current smoking
  - 33.8% reported former smoking
  - 41.4% reported never smoking (Reyes-Guzman et al., 2025)
- Among adults who reported ever using nicotine pouches,1.8% had never used tobacco products before using pouches (Delnevo et al, 2025)
- Daily nicotine pouch use was most common among adults who recently quit other tobacco products, particularly smokeless tobacco products and combusted cigarettes (Delnevo et al., 2025)

Sales data

- ZYN was the most popular nicotine pouch brand at the time of TUS-CPS 2022-2023 data collection (Majmundar et al., 2022)
- Monthly nicotine pouch sales more than tripled from 2021 to 2024 (He et al., 2025)

PMTA Patterns of Use Study

Study Summary

- Cross-sectional retrospective survey
  - 1,266 respondents using ZYN (with or without other tobacco products)
  - 733 respondents using other tobacco products only
- 10-week prospective observational study
  - 346 participants using ZYN and 196 participants using other tobacco products only

Study Findings

- Among participants using ZYN, the proportion who also used combusted cigarettes declined from 15.9% to 8.1% over the study period
- 24% participants using ZYN completely switched from other tobacco products (combusted cigarettes, moist snuff, snus, e-cigarettes, cigars, or cigarillos) to exclusive use of ZYN
- This study experienced substantial loss to follow up – 49% of participants using ZYN and 54% of participants using other tobacco products only

Youth Prevalence of Use Without the Proposed Claim

National Youth Tobacco Survey (2024)

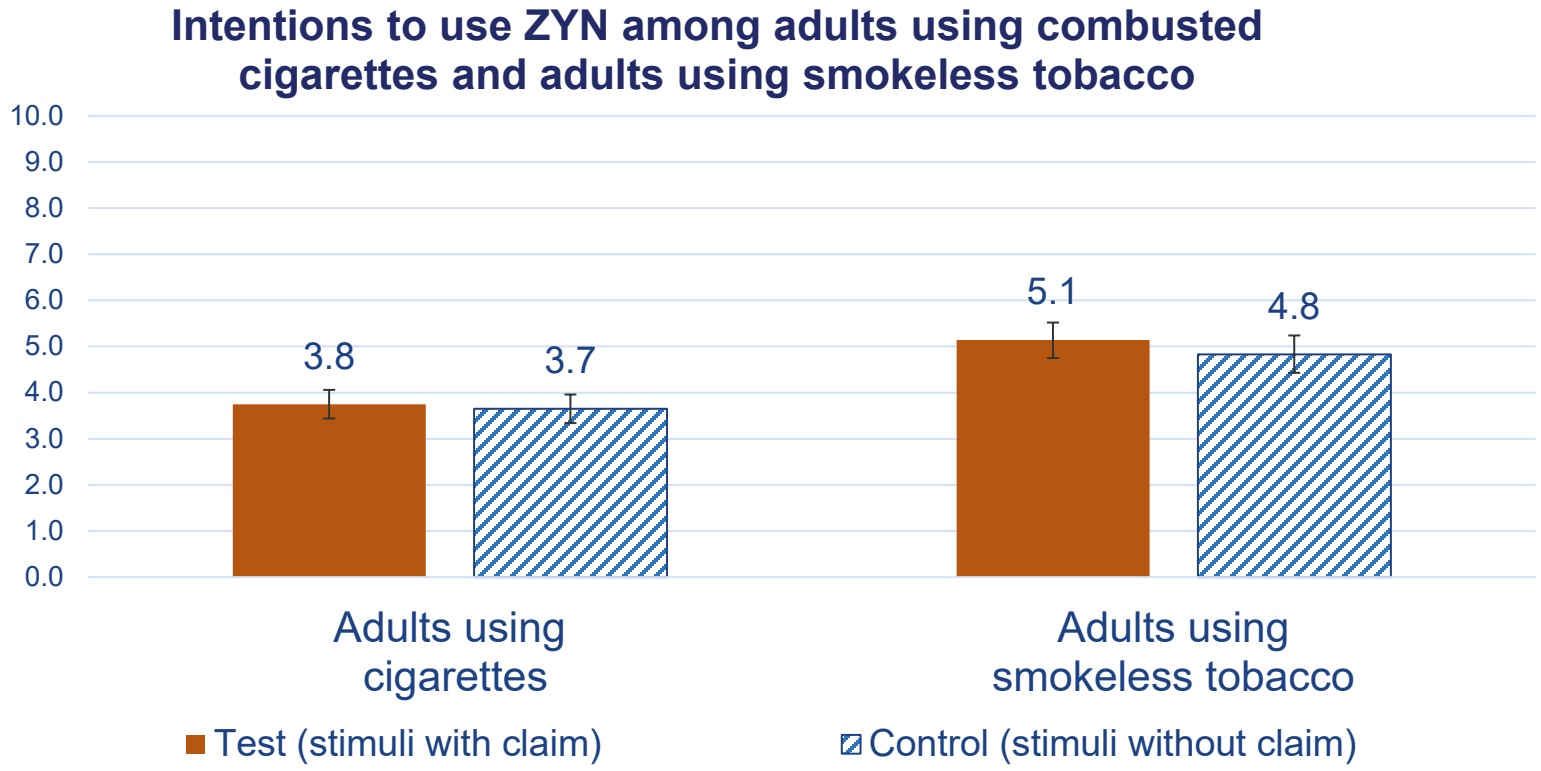
- 1% of US middle school students and 2.4% of US high school students reported current (past 30-day) use of nicotine pouches
- ZYN was the most popular nicotine pouch brand among youth: 35% of middle school students and 72% of high school students who reported current nicotine pouch use reported that ZYN is their usual brand

Monitoring the Future (2024)

- 2.6% of 10th and 12th grade students reported current (past 30-day) nicotine pouch use, up from 1.3% in 2023
- 4.6% of 10th and 12th grade students reported using nicotine pouches in the last 12 months, up from 2.4% in 2023
- 5.4% of 10th and 12th grade students reported ever using nicotine pouches, up from 3.0% in 2023.

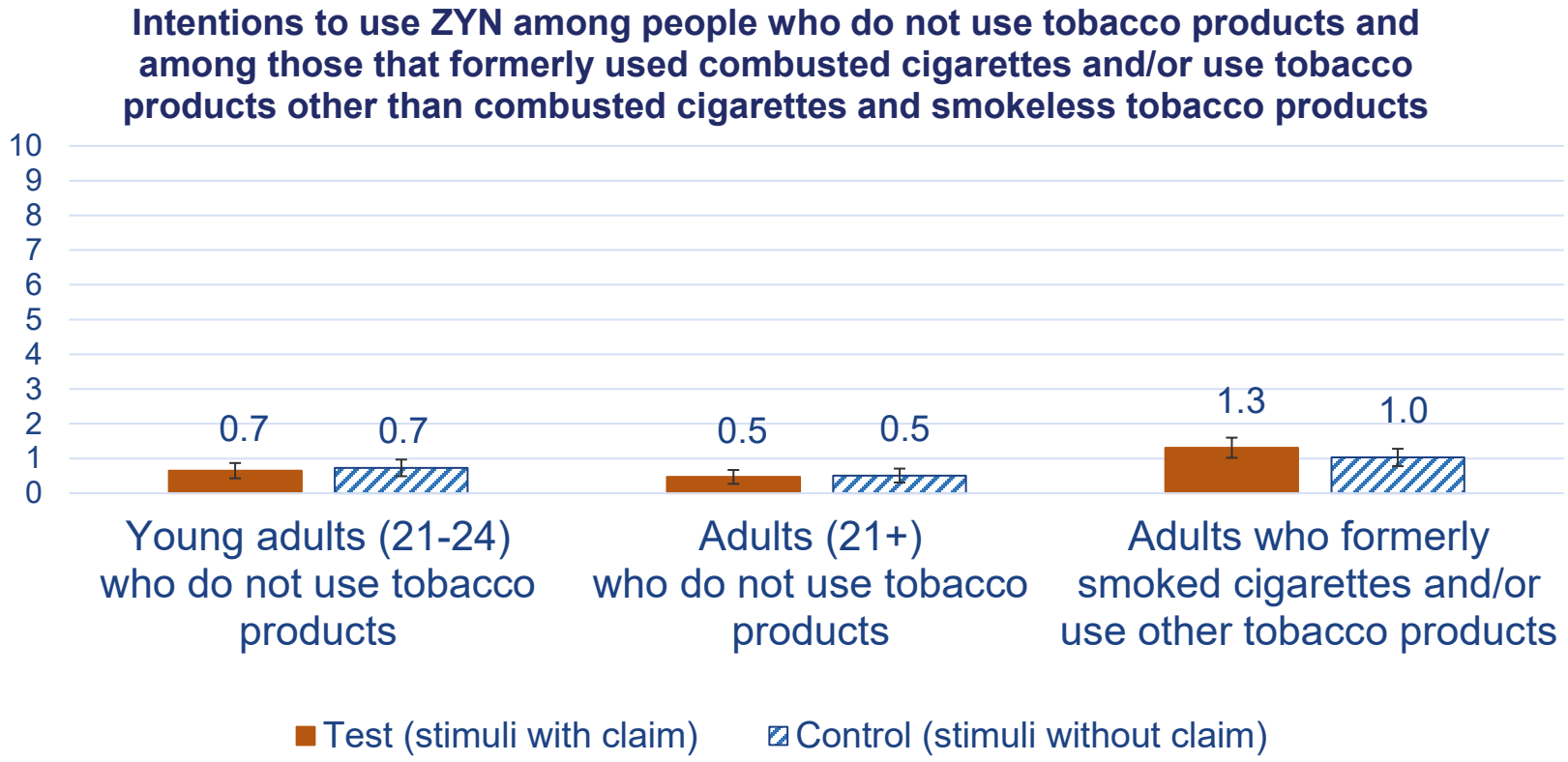
Potential Impact of Proposed Claim on Adults Currently Using Tobacco Products

Findings from the Consumer Perceptions and Likelihood of Use Study



Potential Impact of Proposed Claim on Persons Not Currently Using Combusted Cigarettes or Smokeless Tobacco

Findings from the Consumer Perceptions and Likelihood of Use Study



Summary: Likelihood of Use & Impacts to the Population

- U.S. adult and youth nicotine pouch use prevalence is currently relatively low
- Nicotine pouch sales more than tripled from 2021 to 2024
- Nicotine pouch use is most common among adults who recently quit other tobacco products
- Cross-referenced PMTA Patterns of Use study (without the proposed claim) showed that some participants who used ZYN switched completely from other tobacco products to ZYN at the end of the study
- Consumer Perceptions and Likelihood of Use study showed that:
  - Viewing the proposed claim did not impact intentions to use ZYN among those who were using tobacco products
  - Viewing the proposed claim did not impact intentions to quit smoking among those who use combusted cigarettes
  - Based on the currently available information, intentions to use ZYN were relatively low among those who were not using tobacco products and not impacted by viewing the claim.

Overall Summary

Overall Summary: Accuracy of Proposed Modified Risk Claim

- The evidence suggests the proposed modified risk claim “Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis” is scientifically accurate
- The majority of HPHC biomarkers are lower or below the level of quantification among people who use nicotine pouches as compared to those who use snus or combusted cigarettes
- No long-term studies of health risk of new products due to their relative novelty compared to other categories, but long-term studies of Swedish snus can be considered applicable given the similarities
  - FDA previously concluded that Swedish Match General Snus use is lower risk compared to combusted cigarette smoking for mouth cancer, heart disease, stroke, lung cancer, emphysema, and chronic bronchitis (2019 MRTPA decision summary)

Overall Summary: Consumer Understanding

Consumers correctly understood:

- The risk reduction described in the claim (i.e., ZYN confers lower risk than combusted cigarettes).
- Although conferring lower risk than combusted cigarettes, ZYN still confers health risks.
- How to use ZYN to confer lower risk.

- Misunderstanding of the claim was not in the direction of underestimating risks associated with using ZYN; many consumers overestimated risks associated with ZYN regardless of claim exposure.

Overall Summary: Impact to Population

Among those using tobacco products:

- Nicotine pouch use is most common among adults who recently quit other tobacco products
- 24% of participants who used ZYN completely switched from other tobacco products to ZYN by the end of a 10-week study
- Viewing the proposed claim did not impact intentions to use ZYN among those who were using tobacco products

Among those who do not use tobacco products:

- Youth nicotine pouch use prevalence is currently relatively low
- Among young adults, viewing the proposed claim did not increase intentions to use ZYN

Clarifying Questions

Discussion Topics for the Committee

Discussion Topic 1: Accuracy of Proposed Modified Risk Claim

Background

- The proposed modified risk claim: “Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis”
- The majority of HPHCs are below the level of quantification in ZYN, and the biomarker study of people who use nicotine pouches are consistent with the product chemistry data.
- In absence of long-term health risk studies of nicotine pouches, Swedish snus epidemiological studies show that snus use is lower risk compared to combusted cigarette smoking for mouth cancer, heart disease, stroke, lung cancer, emphysema, and chronic bronchitis.

Discuss whether the proposed modified risk claim is substantiated by the scientific evidence.

Discussion Topic 2: Consumer Understanding and Perceptions

Background

- The applicant provided evidence about whether consumers understood:
  - The risk reduction described in the claim (i.e., ZYN confers lower risk than combusted cigarettes).
  - Although conferring lower risk than combusted cigarettes, ZYN still confers health risks.
  - How to use ZYN to confer lower health risks.

Discuss the available evidence about consumers' understanding of the proposed modified risk claim and their perceptions of ZYN.

Discussion Topic 3: Impact to People Who Use Combusted Cigarettes

Background

- Nicotine pouch use is most common among adults who recently quit other tobacco products
- 24% of participants in the PMTA Patterns of Use study who used ZYN completely switched from other tobacco products to ZYN by the end of a 10-week study
- In the Consumer Perceptions and Likelihood of Use study, viewing the proposed claim did not impact intentions to use ZYN among those who were using tobacco products

If ZYN is marketed with the proposed claim, discuss the evidence regarding the likelihood that people who currently use combusted cigarettes will completely switch to ZYN, and/or will dual use ZYN and combusted cigarettes long-term.

Discussion Topic 4: Impact to People Who Do Not Use Tobacco Products

Background

- Based on the information currently available, youth use of nicotine pouches is relatively low
- Viewing the proposed claim did not increase intentions to use ZYN

If ZYN is marketed with the proposed claim, discuss the evidence regarding the likelihood that persons who do not use tobacco products will start using ZYN.

Supplemental Slides

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