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Subject: Unsolicited PMTA Amendment(s) of Scientific Content for: ZYN® Flagship Varieties¹
FDA STNs: PM0000593 - PM0000612.

Dear Secretary,

Swedish Match USA Inc. ("Swedish Match" or "we") submits this "Amendment" for new tobacco products, collectively the original ZYN Flagship Varieties or ZYN Products, listed in **Table 1** below ("new products"). The Amendment submission is for a group of tobacco products previously submitted as a grouped PMTA submission, FDA STNs: PM0000593 - PM0000612.

Swedish Match is amending the PMTA to provide the most current scientific information that has been collected and/or published since Swedish Match originally submitted the PMTA on March 4, 2020.² Swedish Match is proactively providing these new studies as well as highlighting previously submitted studies to augment the original application demonstrating that marketing a new tobacco product(s) is appropriate for the protection of the public health.

¹ In FDA STNs: PM0000593-PM0000612, the candidate products were referred to as "ZYN." Herein, the candidate products are referred to as "the original ZYN Flagship Varieties" or "ZYN Products."

² In response to clarification questions posed by the FDA, Swedish Match also provided amendments to the ZYN PMTAs on September 24, 2020, and March 7, 2022.

Swedish Match requests to change its submission(s) contents. Specifically, the scientific content for categories including but not limited to Study Report(s), Literature Search, Organized References, Health Risk Investigations and Summary. As part of this Amendment, Swedish Match cross-references existing and updated content in Swedish Match's Tobacco Product Master File, TPMF - FDA STN: (b) (4) and cross-references a nicotine pouch literature review in the (b) (4) TPMF - FDA STN: (b) (4); Letters of Authorization for both TPMFs are included with this Amendment. (b) (4)

This additional content also demonstrates that current, adult tobacco product consumers find the variety of flavors and strengths offered by these products fundamental to their ability to transition from more harmful tobacco products to nicotine pouch products such as ZYN Products. The Amendment is relevant to all amended products in this submission.

Table 1 New Tobacco Products, Original ZYN Flagship Varieties

New Product Name and Strength	Item no.	STN
ZYN Cool Mint 3 mg	900510	PM0000593
ZYN Cool Mint 6 mg	900520	PM0000594
ZYN Peppermint 3 mg	901510	PM0000595
ZYN Peppermint 6 mg	901520	PM0000596
ZYN Spearmint 3 mg	902510	PM0000597
ZYN Spearmint 6 mg	902520	PM0000598
ZYN Wintergreen 3 mg	903510	PM0000599
ZYN Wintergreen 6 mg	903520	PM0000600
ZYN Citrus 3 mg	907510	PM0000601
ZYN Citrus 6 mg	907520	PM0000602
ZYN Coffee 3 mg	904510	PM0000603
ZYN Coffee 6 mg	904520	PM0000604
ZYN Cinnamon 3 mg	906510	PM0000605
ZYN Cinnamon 6 mg	906520	PM0000606
ZYN Smooth 3 mg	914510	PM0000607
ZYN Smooth 6 mg	914520	PM0000608
ZYN Chill 3 mg	920510	PM0000609
ZYN Chill 6 mg	920520	PM0000610
ZYN Fresh 3 mg ³	921510	PM0000611
ZYN Fresh 6 mg ³	921520	PM0000612

³ On December 1, 2020, Swedish Match provided the FDA with notification of a product name/label change for ZYN Fresh 3 mg (PM0000611) and ZYN Fresh 6 mg (PM0000612). The newly named tobacco products (ZYN Menthol 3 mg and ZYN Menthol 6 mg) are identical to currently marketed tobacco products and are simply a name/label change not requiring a separate path to market application. See (b) (4) for complete details.

FDA Form 4057a – Premarket Tobacco Product Application Amendment and General Correspondence Submission(s) is included for each new tobacco product.

The Amendment contains non-public, trade secret, proprietary and confidential information that is protected under state and federal law from public disclosure. Swedish Match reserves the right to redact information it considers to be confidential prior to any part of the Amendment being made public. This information should therefore be handled in accordance with the security procedures adopted by the FDA in connection with enforcement of the FD&C Act.

If further information is required, please contact me.

Sincerely yours,

(b) (6)

Gerard J. Roerty, Jr., Esq.
Vice President, General Counsel & Secretary
Swedish Match USA, Inc.

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Sincerely yours,

Gerard J. Roerty, Jr., Esq.
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Acronyms

APPH	Appropriate for the Protection of Public Health
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CTP	Center for Tobacco Products
ENDS	Electronic Nicotine Delivery Systems
FDA	Food and Drug Administration
FD&C	Food, Drug, and Cosmetic
LOU	Likelihood of Use
mg	Milligrams
MGO	Marketing Granted Order
NYTS	National Youth Tobacco Survey
PMTA	Premarket Tobacco Product Application
POU	Patterns of Use
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STN	Submission Tracking Number
TNP	Tobacco and Nicotine Product
TPMF	Tobacco Product Master File
TPPI	Tobacco Product Perceptions and Intentions
U.S.	United States
UTUS	Underage Tobacco Use Study

MODULE 1 ZYN FLAGSHIP PMTA AMENDMENT

1.0 Integrated Summary

In this Premarket Tobacco Product Application (PMTA) Amendment, Swedish Match USA, Inc., herein referred to as Swedish Match, provides new data and an expanded discussion of previously submitted studies supporting that the original ZYN® Flagship Varieties⁴ (Chill, Cinnamon, Citrus, Coffee, Cool Mint, Fresh/Menthol⁵, Peppermint, Smooth, Spearmint, Wintergreen, each in 3 mg and 6 mg nicotine strengths) are appropriate for the protection of public health (APPH). The bundled PMTAs and previous Amendments are collectively referred to as the original ZYN Flagship PMTA.

1.0.1 Introduction

On March 4, 2020, Swedish Match filed PMTAs for the original ZYN Flagship Varieties referenced in **Table 1** of the Cover Letter. Since then, more information has become available, including the most current scientific information. This information continues to demonstrate that marketing the new tobacco products is APPH. Swedish Match is filing this Amendment to provide this information to the Food and Drug Administration (FDA) in its review. We are proactively providing new studies as well as highlighting previously submitted studies to augment the original application demonstrating that marketing the new tobacco products is APPH.

Since the initial 2020 application, newly available internal and external studies continue to demonstrate that a marketing order for the new tobacco products would provide a net benefit for public health and, just as importantly, outweigh any known risks. This Amendment provides a robust and compelling assessment of the newly available scientific research as well as a further contextualization of the new tobacco products within this developing framework. Throughout the narrative, we identify and provide annotated bibliographic discussions of the government-managed and nationally representative surveys, external public health studies, and our own internal assessments. This information is presented in the corresponding sections as follows:

- **Section 1.1** ZYN Flagship Varieties User Profile Study ((b) (4))
- **Section 1.2** ZYN Flagship Varieties Likelihood of Use [LOU] Study ((b) (4))
- **Section 1.3** ZYN Flagship Varieties Patterns of Use (POU) Study ((b) (4))
- **Section 1.4** Recent Findings from National Youth Tobacco Survey (NYTS) – Absence of Appeal and Uptake of Nicotine Pouches Among Youth
- **Section 1.5** Population Modeling and Analysis
- **Section 1.6** Literature Review
- **Section 1.7** Integrated Conclusion

Swedish Match has incorporated studies and information related to ZYN Products into the Swedish Match tobacco product master file (TPMF) – FDA STN: ((b) (4)) For purposes

⁴ In FDA submission tracking numbers [STNs]: PM0000593-PM0000612, the candidate products were referred to as “ZYN.” Herein, the candidate products are referred to as “the original ZYN Flagship Varieties” or “ZYN Products.”

⁵ ((b) (4))

. See ((b) (4))

for complete details.

⁶ ((b) (4))

of this Amendment, Swedish Match summarizes and highlights key findings pertinent to the original ZYN Flagship Varieties products and population health herein; full details are provided within the referenced TPMF (Table 1.0.1).

The conclusions from the ZYN Flagship Varieties LOU Study (i.e., Section 1.2) and ZYN Flagship Varieties actual use studies (i.e., Section 1.1 and 1.3) demonstrate:

- ...the variety of flavors and strengths available to current users of tobacco products, including users of combustible products, who switch to ZYN Products is important: recent systematic literature reviews conclude that reduced-risk products with nicotine delivery closer to traditional tobacco products and in a variety of flavors are associated with switching away from combusted products (Gades, Alcheva, Riegelman, & Hatsukami, 2022);
- ...current consumers of tobacco products are switching to various flavors but not to any flavor in particular: diverse flavor offerings are an important component of user satisfaction – smokers who switch tend to favor nontobacco flavors (Gentry, Ward, Dawkins, Holland, & Notley, 2020);
- ...nonusers of tobacco products do not indicate intentions to initiate or reinstate with these products (i.e., ZYN Flagship Varieties LOU Study);
- ...youth do not demonstrate interest in these products. This is further supported by recent NYTS data demonstrating an absence of appeal and uptake of nicotine pouches among youth (i.e., 2021-2022 NYTS Analytics (Gentzke et al., 2022; Kramer et al., 2023; Park-Lee et al., 2022; Speciale, Rao, Yang, & Nugent, 2023)).

Table 1.0.1 below outlines the internal and external study reports we have accumulated and assessed for the purposes of this Amendment. In each of these studies, the evidence reinforces these above conclusions.

Table 1.0.1 Index of Population Health Studies Related to the Original ZYN Flagship Varieties

Research	Contents	Study Location in the (b) (4)	Section in This Amendment	Location in PMTA
ZYN Flagship Varieties User Profile Study	(b) (4) - ZYN® User Profile Study Report	(b) (4)	Section 1.1	NA
	(b) (4) - ZYN® User Profile Study Report Post-Hoc Analysis			
ZYN Flagship Varieties LOU Study	ZYN Likelihood of Use Study (b) (4) *		Section 1.2	g-6-human-health-impact-eval-sum
ZYN Flagship Varieties POU Study	ZYN Patterns of Use Study (b) (4)		Section 1.3	g-6-human-health-impact-eval-sum
	Post-Hoc Flavor Analysis: Addendum to Study Report (b) (4)			deficiency-response-ltr-092420ab
	Post-Hoc Strength Analysis: Addendum to Study Report (b) (4)			NA
Recent Findings from NYTS	Absence of Appeal and Uptake of Nicotine Pouches Among Youth	NA	Section 1.4	NA
Population Modeling and Analysis	Estimating the Public Health Impact From Introducing Tobacco Leaf-Free Nicotine Pouches Into the U.S.	(b) (4)	Section 1.5	NA
Comprehensive Literature Review	Nicotine Pouch Literature Review	NA	Section 1.6 and the (b) (4)	NA

* Swedish Match previously conducted this tobacco product perceptions and intentions (TPPI) study entitled "ZYN® Likelihood of Use Study" (b) (4). This study is referred to in this Amendment as the "ZYN Flagship Varieties LOU Study" but may also have been referred to as "Consumer Research Study (b) (4) (Likelihood of Use)" or (b) (4) LOU Study".

¹ The letter of authorization for the (b) (4) TPMF can be found in the (b) (4)

Green highlighting indicates new studies; blue highlighting indicates existing studies.

The new information provided and referenced in this Amendment is hereby incorporated by reference to the administrative record of the new tobacco products listed in **Table 1** of the Cover Letter.

In addition to assessments measuring the likelihood of use of ZYN Products, we also provide data from actual consumer use. These actual use studies included in this Amendment take the form of analytics of validated, government-managed, and nationally representative surveys; external assessments conducted by respected public health organizations; as well as studies from both industry and nonindustry sources. For each respective study, we provide discussions and conclusions, which continue to demonstrate that the new tobacco products do not appeal to youth/young adults or nonusers of tobacco and nicotine products (TNPs). Further, this Amendment provides detailed, annotated bibliographic evidence that supports a net benefit to public health outweighing any known risks.

- Current, adult tobacco product consumers use diverse product options (strengths and flavors) to switch away from more harmful products:
 - ZYN Product consumers had a history of more harmful tobacco product use, and many reduced cigarette smoking, completely switched to ZYN Products, or quit all TNP use altogether;
 - Findings from the ZYN Flagship Varieties POU Study ((b) (4)) support the conclusion that users of traditional tobacco products, such as smokers and smokeless tobacco users, are willing to try and continue using ZYN Products, specifically in substitution for their other tobacco products;
 - A recent systematic literature review concluded that reduced-risk products with nicotine delivery closer to traditional tobacco products and in a variety of flavors are associated with switching away from combusted products (Gades et al., 2022);
 - Diverse flavor offerings are an important component of user satisfaction – smokers who switch tend to favor nontobacco flavors (Gentry et al., 2020);
 - Smokers who were ZYN Product users had greater intention to quit smoking than ZYN Product nonusers. The use of ZYN Products did not interfere with a tobacco product user’s intention to quit all tobacco products;
 - Respondents perceived that ZYN Products carry a higher risk of certain adverse health conditions versus using no tobacco products, but lower risk of those health conditions than smoking and/or using smokeless tobacco.
- Nonusers do not show interest in these products:
 - Based on internally and externally collected data, it is clear that ZYN Products attract current, adult tobacco product users and are not attracting nonusers of tobacco products.
 - Almost all ZYN Product users ((b) (4)) were current tobacco product users prior to first using ZYN Products, and at the time of starting ZYN Product use, ((b) (4)) of the users reported smoking cigarettes ((b) (4)), and ((b) (4)) of the users reported using moist snuff ((b) (4)).

- Youth do not demonstrate interest in these products:
 - NYTS data continue to demonstrate an absence of appeal and uptake of nicotine pouches among youth. The overall use prevalence for United States (U.S.) youth was approximately 1%.⁷
 - Published literature supports the finding that nicotine pouch uptake is low among youth.
 - Estimates from the Altria Client Services Underage Tobacco Use Study (UTUS), a repeated cross-sectional survey collecting data on underage tobacco use on a quarterly basis, were similar to those based on NYTS data (Cheng, Vansickel, & Largo, 2023).
 - The lack of substantial uptake is noteworthy, particularly among underage young adults who are not well covered among school-based surveys like NYTS. Nicotine pouch use estimates remained low throughout the May 2020 – August 2022 study period at less than 0.5% among youth (ages 13-17) and 1.7% or less among underage young adults (ages 18-20).

These important factors amount to population and individual level benefits that would be associated with ZYN Products' availability in the market. The information provided and referenced in this Amendment contains scientific evidence demonstrating that the benefits associated with ZYN Products' availability in the market would outweigh any known risks. Accordingly, a marketing order for the original ZYN Flagship Varieties would be APPH.

1.0.2 Value of Flavors in Moving Consumers Down Continuum of Risk

FDA has acknowledged that consumers need a variety of product formats, flavors, and nicotine strengths to move down the continuum of risk (FDA, 2017, 2019). Products must also have both “high appeal and satisfaction but low toxicity ... such as Swedish-type snus, which has successfully displaced cigarettes in Sweden” (Abrams et al., 2018). The variety of the ZYN Product Line is intended to provide sufficiently appealing products to encourage current tobacco users to move down the continuum of risk.

To ensure a variety of sufficiently appealing products, Swedish Match is seeking a marketing order for the original ZYN Flagship Varieties to encourage current, adult TNP users to move down the continuum of risk. Thus, the ZYN Products minimize risk by providing a low toxicity product that is still appealing to tobacco users (e.g., satisfying nicotine delivery with appropriate/acceptable abuse liability, low social barrier to adoption [socially acceptable to adults], variety of flavors and nicotine strengths). Further, since traditional smokeless tobacco products are available in many varieties, offering ZYN Products in the same or similar varieties could help these users transition to products that are lower on the continuum of risk. This rationale is in line with a recent systematic literature review concluding that the availability of reduced-risk products with nicotine delivery closer to traditional TNPs and in a variety of flavors is associated with switching away from combusted products (Gades et al., 2022). Similarly, in states and localities that restrict or ban the availability of flavored reduced-risk products, economic analysis indicates an increase in the sale of combusted cigarettes (Friedman, Liber, Crippen, & Pesko, 2023). Several articles have concluded that the use of more than one flavor of product was common

⁷ Based on surveys of middle and high school students, overall use prevalence for U.S. youth was approximately 1% (2021: 0.76% [95% CI: 0.54% - 0.98%]; 2022: 1.06% [95% CI: 0.74% - 1.38%]; see also Gentzke et al. (2022) and Park-Lee et al. (2022)). Frequent pouch use (on 20 or more of the past 30 days) was rare in both 2021 and 2022 estimates; the 2021 estimate was 0.13% (95% CI: 0.06% - 0.20%) and the 2022 estimate was 0.27% (95% CI: 0.19% - 0.36%) of U.S. youth.

among users of reduced-risk products and could potentially lead to greater rates of switching away from combusted cigarettes (Farsalinos et al., 2013; Gentry et al., 2020; Romijnders et al., 2019). Collectively, these findings support that the candidate products are APPH.

Additionally, the original ZYN Flagship Varieties provide current, adult TNP consumers access to a range of nicotine options so that users can find a ZYN Product that provides a satisfying nicotine experience and, therefore, reduce barriers to trying and switching to reduced-risk products. The value of efficient and sufficient nicotine delivery, such as from the original ZYN Flagship Varieties, has been well summarized by current Center for Tobacco Products (CTP) Center Director Brian King, PhD, during an interview in which he makes clear that reduced-risk products that efficiently deliver nicotine “hold some public health promise in terms of giving smokers enough nicotine that they would transition completely” (Perrone, 2022).

While the current tobacco marketplace features numerous varieties (strengths and flavors) of nicotine pouches, NYTS 2021 and 2022 ([Section 1.4](#)) data continue to demonstrate an absence of appeal and uptake of nicotine pouches among youth. Of the youth surveyed in 2021, only 0.8% reported being current users of nicotine pouches, and these numbers fall below 0.1% for fruit and alcoholic drink varieties of nicotine pouches (Gentzke et al., 2022; Kramer et al., 2023; Speciale et al., 2023). Estimates from the Altria Client Services UTUS, a repeated cross-sectional survey collecting data on underage tobacco use on a quarterly basis, were similar to those based on NYTS data (Cheng et al., 2023). Nicotine pouch use estimates remained low throughout the May 2020 - August 2022 study period at less than 0.5% among youth (ages 13-17) and 1.7% or less among underage young adults (ages 18-20). While the authors appropriately recommend continued monitoring given moderate levels of product awareness, the lack of substantial uptake is noteworthy, particularly among underage young adults who are not well covered among school-based surveys like NYTS. Additionally, our TPPI study (i.e., LOU study) indicates almost no interest in the original ZYN Flagship Varieties by either young adult or adult nonusers of tobacco products.

Further, Swedish Match is also aware of marketing granted orders (MGOs) for mint-flavored oral products, including VERVE® Discs Blue Mint, VERVE Discs Green Mint, VERVE Chews Blue Mint, and VERVE Chews Green Mint (FDA, 2021a). FDA also demonstrated acceptance of flavored oral tobacco products in the General Snus Technical Project Lead review, which reads,

The proposed products are reported to have flavors such as mint, wintergreen, or tobacco character with citrus. While flavored smokeless tobacco products are a potential concern of youth initiation, these proposed flavors are consistent with traditionally available [smokeless tobacco] flavors and are not novel flavors that likely increase appeal to youth. Overall uptake of snus products, including among youth in the US, is low even with such flavors available in currently marketed products and is unexpected to dramatically increase with the marketing of the PMTA products at this time (FDA, 2015).

Therefore, based on historical precedent and FDA’s MGOs, traditional oral products encompass a wide range of flavors, many of which FDA has found to be APPH. The original ZYN Flagship Varieties are available in flavors that have been found in traditional smokeless tobacco (e.g., moist snuff and snus) for decades and should be considered in line with FDA’s MGOs.

Considering the acceptability of flavored smokeless products amongst current, adult TNP users and the evidence of minimal youth appeal and uptake of such products, Swedish Match amends this PMTA to provide discussions of rigorous scientific investigations to further support that the original ZYN Flagship Varieties are APPH. Based on the evidence in this PMTA and associated Amendments, Swedish Match believes marketing of the candidate

products will ensure continued access to reduced-risk alternatives to encourage current, adult TNP users to transition down the continuum of risk without appealing to nonusers or youth.

1.0.3 Consumer Use Behaviors

Section 910(c)(4) of the Food, Drug, and Cosmetic (FD&C) Act requires that the FDA consider "...the risks and benefits to the population as a whole, including users and nonusers of tobacco products, and taking into account:

- the increased or decreased likelihood that existing users of tobacco products will stop using such products and
- the increased or decreased likelihood that those who do not use tobacco products (including youth and young adults) will start using such products" (FDA, 2021b).

As part of the Premarket Tobacco Product Application and Recordkeeping Requirements (PMTA Rule), FDA requested that applicants provide information summarizing the degree to which the candidate products would likely be APPH.

In this Amendment, Swedish Match discusses the impact of the original ZYN Flagship Varieties on population health, including the potential risks and benefits to current TNP users and nonusers, to provide expanded discussion and new data supporting that the original ZYN Flagship Varieties (i.e., candidate products) are APPH. The evidence in this Amendment is intended to supplement the original ZYN Flagship PMTA submission.

Since the submission of the original ZYN Flagship PMTA, Swedish Match has conducted additional studies that have contributed to the narrative around consumer use patterns of the original ZYN Flagship Varieties products and further support that the candidate products are APPH. These are referred to as "new studies" below. In addition, Swedish Match includes in this Amendment an expanded discussion of studies that were previously submitted in the original ZYN Flagship PMTA. These are referred to as "expanded discussion of previously submitted ZYN Product Studies" below. Specifically, Swedish Match discusses the following studies in this Amendment:

- **New Studies**
 - **ZYN Flagship Varieties User Profile Study ((b) (4)) (Section 1.1)** is a new study that indicates that use frequency is not dependent on user choice of flavor variety or nicotine strength. The results also indicate a majority of ZYN Product users reported either stopping cigarette use (no past-30-day cigarette use) or a decrease in cigarette use. Thus, the ZYN Products not only allow users to transition to a product lower on the continuum of risk, but they have the demonstrated potential for users to reduce or abstain from cigarette use. Though use frequency and use patterns were similar across flavored and unflavored varieties, a notably larger percentage of subjects sought out flavored varieties. These findings demonstrate that ZYN Product users try, currently use, and favor a variety of flavors and nicotine strengths across the ZYN Product Line, and that smokers who use ZYN Products either completely switch away from or reduce their use of cigarettes. These collective findings suggest offering diverse flavor varieties and nicotine

strengths are important components of user satisfaction, thus, allowing cigarette and/or other TNP users the opportunity to transition to a product lower on the continuum of risk.

- **Recent NYTS findings indicate an absence of appeal and uptake of nicotine pouches among youth (Section 1.4).** NYTS has included questions regarding nicotine pouch use for two years (2021 and 2022, the two most recent NYTS data collections currently available). NYTS data continue to demonstrate an absence of appeal and uptake of nicotine pouches among youth, augmenting the results on nicotine pouch use among U.S. youth from other published literature. More recently published literature continues to support the finding that nicotine pouch uptake is low among this important unintended user group.
- **The population health impact modeling study of ZYN Products (Section 1.5)** is a new study that used product-related mortality estimates to investigate the public health impact of introducing the ZYN Product Line over the time period of 2000-2050. Over the 50 years after introduction of the ZYN Product Line, deaths at ages 35 to 84 due to product use are estimated to decrease by about 700,000 in the total U.S. population. The study provides evidence that the introduction of the ZYN Product Line to the U.S. market would be APHP.
- **An independent, comprehensive review of the peer-reviewed scientific, medical, and public health literature for oral nicotine pouch products (Section 1.6)** was commissioned by Swedish Match and conducted by (b) (4). In the original PMTA, Swedish Match submitted systematic literature reviews of snus. At the time, the available literature on nicotine pouches was very limited. Swedish Match is now amending the PMTA to include this comprehensive literature review of nicotine pouches with the purpose of providing the FDA "all relevant health risk data to determine whether permitting the marketing of the product would be appropriate for the protection of the public health." The population health section of the literature review suggests youth and nonusers of tobacco products are unlikely to become nicotine pouch users, nicotine pouches appeal to current TNP users, and people who have tried nicotine pouches seem interested in using them to reduce or quit TNP use.
- **Expanded Discussion of Previously Submitted ZYN Product Studies**
 - **The ZYN Flagship Varieties LOU Study (b) (4) (Section 1.2)** demonstrates that never users and former users of TNPs do not find the original ZYN Flagship Varieties appealing and are unlikely to initiate or reinstate TNP use. Additionally, current TNP users have a low-to-moderate likelihood of use of the original ZYN Flagship Varieties and consumers generally have their own individual flavor preferences, supporting the need for a variety of reduced-risk products to move current TNP users down the continuum of risk. Additionally, an oversampling of young adults was used as a proxy for youth perceptions and intentions; findings suggest the candidate products are not appealing to this population. The original ZYN Flagship Varieties create a more diverse market by offering a range of options to current, adult tobacco consumers as they transition to products with less risk.
 - **The ZYN Flagship Varieties POU Study (b) (4) (Section 1.3)** indicated that use of cigarettes or moist snuff decreased over (b) (4) in ZYN Product users but remained consistent among ZYN Product nonusers. Regardless of the variety used,

about a quarter of the ZYN Product users reported completely substituting ZYN Products in place of other TNPs, and some of the ZYN Product users had quit all TNP use by (b) (4) of the prospective part of the study. These results demonstrate that, over time, a sizeable percentage of TNP users reduce their TNP use, completely switch to ZYN Products, or quit TNP use altogether.

Collectively, these studies demonstrate that the original ZYN Flagship Varieties provide population and individual level benefits by offering a variety of satisfying, reduced-risk options to current, adult TNP users, without appealing to never and former users of TNPs or youth. Further, Swedish Match anticipates that postmarket surveillance studies evaluating consumer switching would yield similar findings to the user profile and POU studies summarized herein. Swedish Match is committed to discussing appropriate postmarket surveillance requirements for the candidate products with FDA as needed.

Based on the collective evidence within the original ZYN Flagship PMTA and this Amendment, the original ZYN Flagship Varieties are part of a diverse marketplace that enables current, adult TNP users to move to products lower on the continuum of risk, without appealing to nonusers or youth. Thus, granting of a marketing order for the original ZYN Flagship Varieties would be APPH.

1.1 ZYN Flagship Varieties User Profile Study (b) (4)

Swedish Match commissioned a user profile study to characterize use behavior and product preferences of ZYN Product users. Swedish Match refers to the ZYN User Profile Study (b) (4) and ZYN User Profile Study (b) (4), collectively, as the ZYN Flagship Varieties User Profile Study. For the complete report, detailing the methodology and findings, see (b) (4).

The cross-sectional survey study recruited participants directly from Swedish Match's database of known ZYN Product purchasers who had opted in to receive communications from Swedish Match related to ZYN Products. A total of (b) (4) respondents completed the survey and were included in the analytic dataset. The results of the ZYN Flagship Varieties User Profile Study were stratified by nicotine strength and flavor varieties. The post-hoc analysis was conducted to determine frequency of use of ZYN Products, as well as changes in cigarette consumption, based on ZYN Product users' preferred flavored and unflavored original ZYN Flagship Varieties (Section 1.1.1) and based on preferred nicotine strength (Section 1.1.2). The study demonstrates that users try, currently use, and favor a variety of flavors across the ZYN Product Line, and that smokers who use ZYN Products either completely switch from or reduce their use of cigarettes. Thus, ZYN Products not only allow users to transition to a product lower on the continuum of risk, but they have the demonstrated potential for users to reduce or abstain from cigarette use.

1.1.1 Preferred Variety Results and Discussion

Frequency of use results (Table 1.1.1) indicated that ZYN Product users used a comparable number of pouches per day across all flavored and unflavored varieties (b) (4). This indicates that use frequency is not dependent on flavor variety choice.

The study also investigated changes in cigarette consumption (Table 1.1.2) among ZYN Product users who reported cigarette use at the time of their initiation of ZYN Product use. Across all varieties, the majority (b) (4) of ZYN Product users reported at least 50% decreased combustible cigarette consumption (b) (4) or have

stopped smoking completely (b) (4) since starting to use ZYN Products. Regardless of flavor choice, (b) (4) of ZYN Product users completely stopped smoking, and (b) (4) of ZYN Product users who are still smoking reported a decrease in cigarette use by more than 50% since starting ZYN Product use. These findings indicate a potential for cigarette use reduction and abstinence (defined as no past-30-day use), allowing cigarette users the opportunity to transition to a product lower on the continuum of risk. The similarity in reduction and abstinence percentages across ZYN Product varieties further indicates that flavored and unflavored varieties have similar use patterns. Noteworthy, fewer consumers prefer unflavored varieties (i.e., ZYN Chill and Smooth) compared to flavored varieties. Therefore, the results indicate flavored products may have a greater population impact (greater number of users discontinue or decrease their use of combustible cigarettes) than unflavored varieties, as flavored products are preferred by a greater number of ZYN Product users.

Table 1.1.1 Frequency of Use by Preferred ZYN Product Varieties

	Cool Mint	Spearmint	Peppermint	Wintergreen	Cinnamon	Coffee	Citrus	Chill	Smooth
	N*	N*	N*	N*	N*	N*	N*	N*	N*
	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev
N =	(b) (4)								
Percent of days that ZYN Products are used									
Average number of ZYN Products used daily by everyday users									
Average number of ZYN Products used on some days									

*Number of non-missing responses

Percent of days where ZYN Products are used is 100% for everyday users, and for someday users is calculated as the number of days ZYN Products were used divided by the past-30-day period. The maximum value of (b) (4) (for Peppermint users) is equivalent to (b) (4), and the minimum value of (b) (4) (for Cinnamon users) is (b) (4).

Average number of ZYN Products used on some days is the reported average number of pouches used on days where ZYN Products were used in the past 30 days.

Source: ZYN User Profile Study (b) (4)

Table 1.1.2 Change in Cigarette Consumption by Preferred ZYN Product Varieties

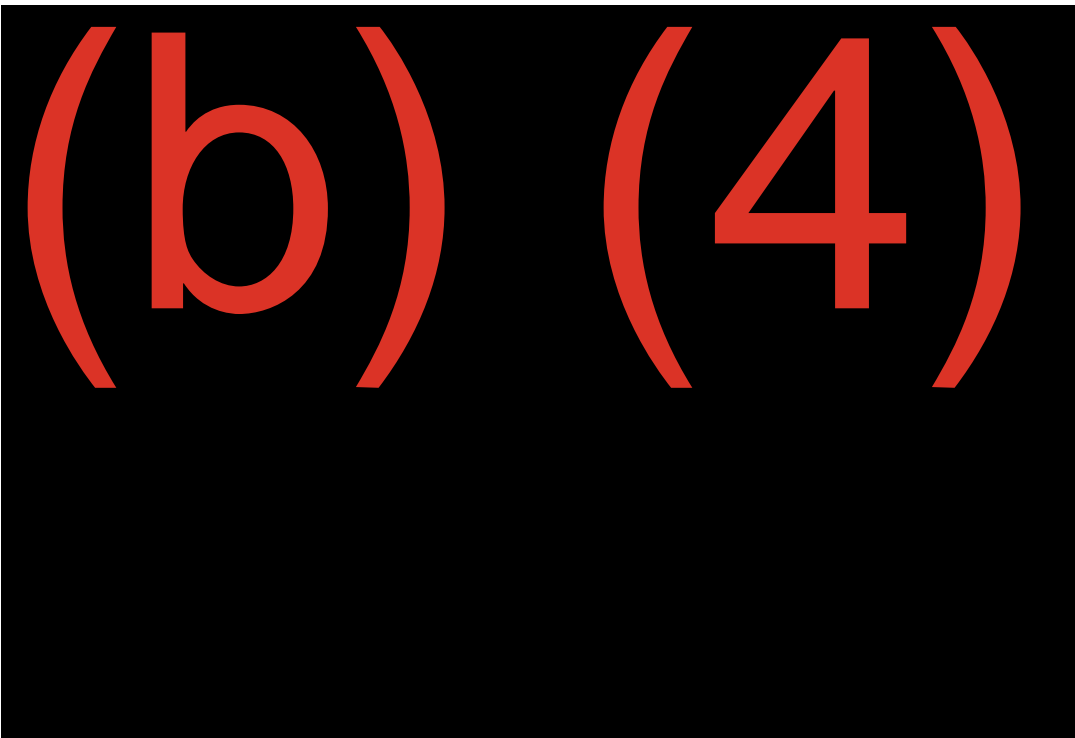
	ZYN Product Flavors Currently Used								
	Cool Mint	Spearmint	Peppermint	Wintergreen	Cinnamon	Coffee	Citrus	Chill	Smooth
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
N =	(b) (4)								
N* reporting having smoked cigarettes at the start of ZYN Product use									
No, I have not changed my cigarette consumption (%)									
Yes, I have decreased my consumption by more than 50% (%)									
Yes, I have decreased my consumption by 50% or less (%)									
Yes, I have increased my cigarette consumption by more than 50% (%)									
Yes, I have increased my cigarette consumption by 50% or less (%)									
Smoked at the start of ZYN, but not in the past 30 days									
Don't know (%)									

*Number of non-missing responses, which is the number of people who smoked at the start of using ZYN Products

Source: ZYN User Profile Study (b) (4)

Though use frequency and use patterns were similar across flavored and unflavored varieties, the presence of a variety of flavored and unflavored options may be beneficial for TNP users seeking to reduce health risks. **Figure 1.1.1** displays flavor preferences of ZYN Product users. Users were asked what variety they first used or tried, what varieties they have ever used, what varieties they currently use, and their favorite variety. The results demonstrate that ZYN Product users have diverse preferences across the product varieties, as a wide distribution of reported favorite or currently used variety was observed. A smaller percentage of users report trying or using unflavored varieties (i.e., ZYN Chill and Smooth) compared to flavored varieties. Additionally, users tend to try multiple varieties before finding their favorite or current variety. This suggests that diverse variety offerings are an important component of user satisfaction. This is in line with a recently published study of consumer use patterns and flavor preferences in other reduced-risk product categories (Gentry et al., 2020).

Figure 1.1.1 (b) (4)

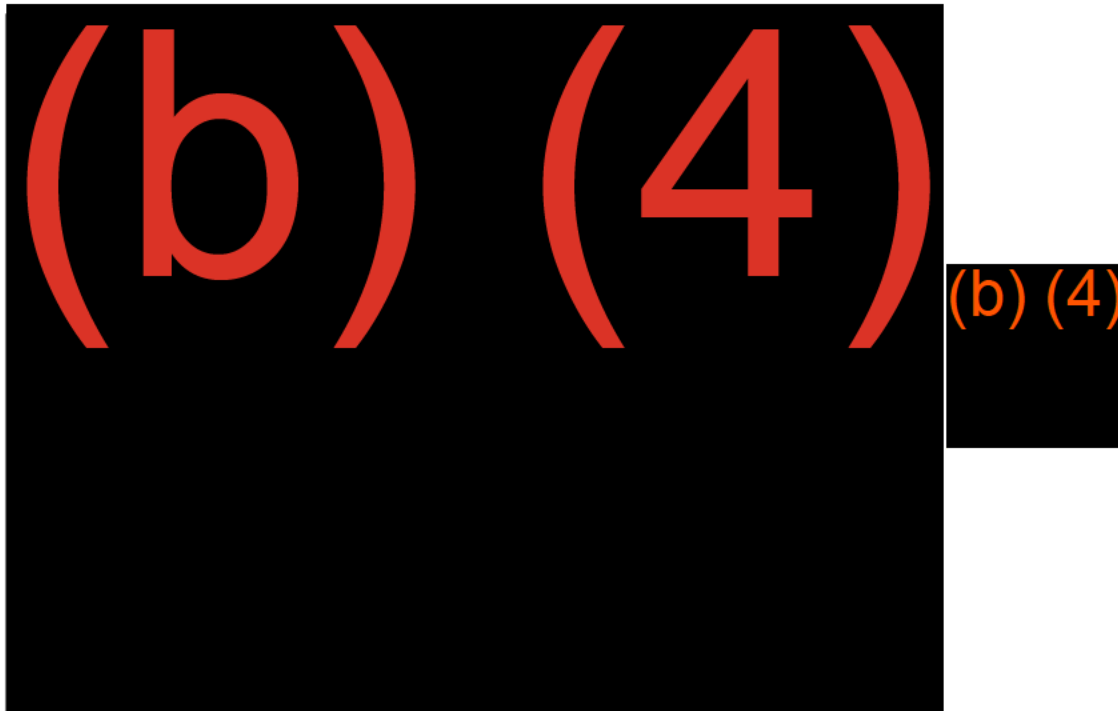


Source: ZYN User Profile Study (b) (4)

1.1.2 Preferred Nicotine Strength Results and Discussion

The nicotine strength preferences of ZYN Product users were stratified by 3 mg and 6 mg nicotine strengths and are shown in **Figure 1.1.2**. The results demonstrate that, regardless of flavor variety, ZYN 6 mg is more often the first used/tried, ever used/tried, currently used, and favorite variety. This finding, coupled with the wide distribution of reported favorite or currently used variety, suggests that ZYN Product users have diverse preferences. Thus, a diverse variety of offerings is an important component of user satisfaction.

Figure 1.1.2 (b) (4)



Source: ZYN User Profile Study (b) (4)

Frequency of use results (Table 1.1.3) indicated that ZYN Product users used a comparable number of pouches per day regardless of preferred nicotine strength (b) (4). This indicates that use frequency is not dependent on preferred nicotine strength.

The study also investigated changes in cigarette consumption (Table 1.1.4) among ZYN Product users who reported cigarette use at the time of their initiation of ZYN Product use, by their preferred ZYN Product nicotine strength. Of the (b) (4) respondents in the study, (b) (4) reported dual use of combustible cigarettes when starting ZYN Products. At the time of the study, of these dual users, over half (b) (4) had not used cigarettes during the past 30 days, and (b) (4) had decreased their cigarette consumption. When examining participants who reported no past-30-day cigarette use, those using ZYN 3 mg exclusively had a discontinuation rate of (b) (4), and ZYN 6 mg users had a similar discontinuation rate of (b) (4). Similar rates of decreasing cigarette consumption were observed among those who exclusively used ZYN 3 mg (b) (4) and those who exclusively used ZYN 6 mg (b) (4). It should be noted that while percentages of quitting or decreasing cigarette use were similar among exclusive ZYN 3 mg or exclusive ZYN 6 mg users, the number of exclusive ZYN 6 mg users (b) (4) is almost three times the number of exclusive ZYN 3 mg users (b) (4). Therefore, the results indicate ZYN 6 mg products may have a greater population impact (greater number of users discontinue or decrease their use of combustible cigarettes). This trend is in line with a recent, randomized clinical trial demonstrating that consumers using alternative products with levels of nicotine delivery closer to their combusted product are more successful at switching to a reduced-risk product (Cobb et al., 2021).

The data also showed that users typically first select what is ultimately their preferred nicotine strength (Figure 1.1.2); that there is no significant difference in ZYN Product pouches used per day between 3 mg exclusive, 6 mg exclusive, or 3 mg and 6 mg users (Table 1.1.3); and that a majority of smokers who start using ZYN Products either quit smoking or decrease their cigarette consumption through use of ZYN Products (Table 1.1.4).

Table 1.1.3 Frequency of Use by Preferred ZYN Product Nicotine Strength

	3 mg Exclusive	6 mg Exclusive	3 mg & 6 mg	Total
	N*	N*	N*	N*
	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev	Mean ± Std Dev
N =	(b) (4)			
Percent of days that ZYN Products are used				
Average number of ZYN Products used everyday				
Average number of ZYN Products used on some days				

*Number of non-missing responses

Percent of days where ZYN Products are used is 100% for everyday users, and for someday users is calculated as the number of days ZYN Products were used divided by the past-30-day period. (b) (4)

Average number of ZYN Product pouches used on some days is the reported average number of pouches used on days where ZYN Products were used in the past 30 days.

Source: ZYN User Profile Study (b) (4)

Table 1.1.4 Change in Cigarette Consumption by Preferred ZYN Product Nicotine Strength

	ZYN Product Nicotine Strengths Currently Used			
	3 mg Exclusive	6 mg Exclusive	3 mg & 6 mg	Total
	n (%)	n (%)	n (%)	n (%)
N =	(b) (4)			
Reported number cigarettes smoked since starting ZYN Product use				
N* CC smokers at start of study				
No, I have not changed my cigarette consumption (%)				
Yes, I have decreased my consumption by more than 50% (%)				
Yes, I have decreased my consumption by 50% or less (%)				
Yes, I have increased my cigarette consumption by more than 50% (%)				
Yes, I have increased my cigarette consumption by 50% or less (%)				
Smoked at the start of ZYN, but not in the past 30 days (so did not see the question)				
Don't know (%)				

*Number of non-missing responses, which is the number of people who smoked at the start of using ZYN Products

Source: ZYN User Profile Study (b) (4)

CC = combustible cigarettes

1.1.3 Light/Medium/Heavy Use Results and Discussion

The frequency of ZYN Product light, medium, and heavy use by exclusive 3 mg users, exclusive 6 mg users, or 3 mg and 6 mg users is shown in Table 1.1.5. The distribution of light, medium, and heavy use frequency among these user groups are similar. Additionally, consumers with higher ZYN Product use frequency were more likely to have reported complete switching or reduction in cigarette use.

Table 1.1.5 Use Frequency for Each ZYN Product Nicotine Strength User Group

	3 mg Exclusive	6 mg Exclusive	3 mg & 6 mg
N	(b) (4)		
Heavy			
Medium			
Light			

(b) (4)

1.1.4 ZYN Flagship Varieties User Profile Study Conclusion

Collectively, the user profile study and post-hoc analysis characterized behavior and preferences, assessed frequency of use, and determined changes in cigarette consumption among current ZYN Product users. Results were stratified by the ZYN Product users' preferred flavored/unflavored varieties as well as preferred nicotine strength.

Regarding preferred flavor varieties, the evidence shows use frequency and use patterns were similar across flavored and unflavored varieties. ZYN Product users used a comparable number of pouches per day across all flavored and unflavored varieties, suggesting use frequency is not dependent on flavor variety choice. Noteworthy, fewer consumers prefer unflavored varieties (i.e., ZYN Chill and Smooth) compared to flavored varieties. Therefore, the results indicate flavored products may have a greater population impact (greater number of users discontinue or decrease their use of combustible cigarettes) than unflavored varieties, as flavored products are preferred by a greater number of ZYN Product users.

Regarding preferred nicotine strength, the evidence shows users typically first select what is ultimately their preferred nicotine strength, and there is no significant difference in ZYN Product pouches used per day between 3 mg exclusive, 6 mg exclusive, or 3 mg and 6 mg users, suggesting use frequency is not dependent on nicotine strength. Further, the distribution of light, medium, and heavy use frequency among the exclusive 3 mg users, exclusive 6 mg users, or 3 mg and 6 mg users are similar. Of note, ZYN 6 mg is more often the first used/tried, ever used/tried, currently used, and favorite variety regardless of flavor variety, suggesting ZYN 6 mg products may have a greater population impact by helping more TNP users transition away from more harmful products.

Regarding changes in cigarette consumption, the results demonstrate a majority of smokers who start using ZYN Products either quit smoking or decrease their cigarette consumption through use of ZYN Products. The cigarette use reduction and abstinence percentages were similar across preferred ZYN Product flavor varieties and nicotine strengths.

Overall, the findings demonstrate that users try, currently use, and favor a variety of flavors and nicotine strengths across the ZYN Product Line, and that smokers who use ZYN Products either completely switch from or reduce their use of cigarettes. These collective findings suggest offering diverse flavor varieties and nicotine strengths are important components of user satisfaction, thus, allowing cigarette and/or other TNP users the opportunity to transition to a product lower on the continuum of risk.

1.2 ZYN Flagship Varieties LOU Study ((b) (4))

This section briefly summarizes the ZYN Flagship Varieties LOU Study ((b) (4)). The ZYN Flagship Varieties LOU Study was a TPPI study that evaluated the perceptions and intentions associated with the original ZYN Flagship Varieties products. The ZYN Flagship Varieties LOU Study found that never users and former users of TNPs do not find the original ZYN Flagship Varieties products appealing, and, thus, that these populations are unlikely to initiate or reinstate TNP use with the original ZYN Flagship Varieties. Additionally, an oversampling of young adults was used as a proxy for youth perceptions and intentions; findings suggest the candidate products are not appealing to this population. The evidence suggests that the original ZYN Flagship Varieties products are most, though only moderately, appealing to current TNP users, particularly those with intent to quit use of combustible cigarettes. Furthermore, the study found that all populations understood the risks associated with use of the original ZYN Flagship Varieties products relative to use of other TNPs and no TNPs.

1.3 ZYN Flagship Varieties POU Study ((b) (4))

This section provides an expanded discussion to further interpret findings from the ZYN POU Study ((b) (4)), that was included in the original PMTA submission, as well as results and discussion of post-hoc analyses conducted on the results from the prospective, ((b) (4)) part of the POU Study (Post-Hoc Flavor Analysis: Addendum to Study Report ((b) (4)); Post-Hoc Strength Analysis: Addendum to Study Report ((b) (4))). Collectively, these studies are referred to as the ZYN Flagship Varieties POU Study.

1.3.1 ZYN POU Study ((b) (4))

The ZYN POU Study ((b) (4)) was a comprehensive, two-part (retrospective and prospective), observational POU study of the original ZYN Flagship Varieties among adult ZYN Product users and nonusers. The purpose of the retrospective part of this study was to evaluate ZYN Product users' and nonusers' past use of TNPs, intention to quit, and perceptions of risk. The purpose of the ((b) (4)), prospective part of the study was to monitor continued use of TNPs and intention to quit TNPs between users and nonusers of the original ZYN Flagship Varieties products. The purpose of the post-hoc analyses was to evaluate the impact of flavors and nicotine strengths on patterns of ZYN Product use. The results indicate that patterns of use are similar across preferred flavor varieties and nicotine strengths tested and suggest that **flavors had little impact on usage patterns and nicotine strength had little impact on pouch usage.**

More specifically, the post-hoc analyses by flavor varieties and nicotine strengths of the original ZYN Flagship Varieties in the POU study indicate that patterns of use and complete substitution of ZYN Products for all other TNPs by the end of the prospective, ((b) (4)) period found minor differences by flavor variety and nicotine strength. Post-hoc analyses of the original ZYN Flagship 3 mg and 6 mg Varieties in the POU study indicate that pouch consumption per day does not differ across nicotine strengths ((b) (4)). Users reported similar percentage of days on which ZYN Products were used and average number of minutes ZYN Product pouches were used. Quitting all TNP use by the end of the prospective period was similar across the flavor varieties and

across nicotine strengths. Complete substitution of TNPs with ZYN Products was similar across flavor varieties but was highest among those who frequently used ZYN Spearmint and ZYN Coffee. These results should be considered with caution due to low sample sizes for some flavors, as well as users being classified based on their most frequently used flavor, as it is possible that ZYN Product users used more than one flavor during the course of the prospective study. Swedish Match anticipates that postmarket surveillance studies evaluating consumer use patterns would yield similar findings. Swedish Match is committed to discussing appropriate postmarket surveillance requirements for the candidate products with FDA as needed.

Similarly, the ZYN User Profile Study and associated post-hoc analysis (Section 1.1) demonstrated that, across the nine tested flavored and unflavored original ZYN Flagship Varieties, the average number of ZYN Product pouches used per day is consistent; the reduction in combustible cigarette use is also similar. Additionally, the percent of days used (b) (4) and pouch consumption were comparable across nicotine strengths.

1.3.1.1 ZYN POU Study (b) (4) Results and Conclusions

A complete description of the study findings is in the ZYN POU Study Report (b) (4) and are summarized below.

The study findings support the conclusion that users of traditional TNPs, such as smokers and smokeless tobacco users, are willing to try and continue using ZYN Products, specifically in substitution for their other TNPs. Collectively, respondents view ZYN Products as riskier than using no TNPs but less risky than smoking or using smokeless tobacco. Specifically, the collective findings revealed that:

- Smokers who were ZYN Product users had greater intention to quit smoking than ZYN Product nonusers.
- ZYN Product users did not reveal intent to quit the ZYN Product itself.
- Respondents perceived that ZYN Products carry a higher risk of certain adverse health conditions versus using no TNPs but lower risk of those health conditions than smoking and/or using smokeless tobacco.
- The retrospective part of the study found that almost all ZYN Product users (b) (4) were current TNP users prior to first using ZYN Products, and at the time of starting ZYN Product use (b) (4) of the users reported smoking cigarettes (b) (4) and (b) (4) of the users reported using moist snuff (b) (4). After an average of five to six months of using ZYN Products, only (b) (4) of the users reported smoking cigarettes (b) (4) and only (b) (4) reported using moist snuff (b) (4) in the last 30 days. Use of other TNPs also declined from weeks prior to using ZYN Products to use in the last 30 days. Even after using ZYN Products for months, cigarette and moist snuff usage continued to trend downward over the observed (b) (4) research period.
- Based on the data, it is clear that ZYN Products attract current TNP users and are not attracting nonusers of TNPs.
- Study findings did not indicate that ZYN Products adversely affects public health. In fact, some results suggested a potential for beneficial effects. For instance, results show nearly all ZYN Product

consumers had a history of more harmful tobacco product use, and many reduced cigarette smoking and/or completely switched to ZYN Products.

- Among ZYN Product users, the reported intention to quit smoking cigarettes tended to increase over the (b) (4) period.
- The number of days per week ZYN Products were used slightly decreased over the (b) (4), although the number of pouches and the duration of use remained unchanged.
- At the first week of the prospective study, around (b) (4) of the ZYN Product users used only ZYN Products, and at the end of the study, the proportion of exclusive ZYN Product users had increased to (b) (4).

1.3.2 Post-Hoc Flavor Analysis: Addendum to Study Report (b) (4)

A post-hoc analysis was performed on the (b) (4), prospective ZYN POU Study (b) (4) to examine ZYN Product patterns of use, reasons for use, and product switching or quitting by flavor varieties. More specifically, the ZYN Product patterns of use (average number of ZYN Product pouches used per day and average number of minutes ZYN Products were kept in the mouth) among ZYN Product users during the prospective, observational period was analyzed by ZYN Product flavor varieties (Cool Mint, Peppermint, Wintergreen, Spearmint, Cinnamon, and Coffee). As it was possible for participants to use multiple flavors throughout the (b) (4) period, they were grouped according to their most frequently used flavor during the (b) (4) period.

The distribution of most frequently used flavor varieties during the prospective, (b) (4) study is shown in Table 1.3.1. The number of pouches used per day and average number of minutes ZYN Products were used are shown in Table 1.3.2 and Table 1.3.3, respectively. The distribution in flavor variety most frequently used, where no flavor was chosen by more than (b) (4) of users, suggests that offering a variety of flavor options is important for achieving the marked reduction in cigarette and moist snuff use observed. While the number of pouches used per day varied slightly, Swedish Match believes this may be a reflection of individual users' personal preferences, as the number of respondents was low. Further, as described in Section 1.1, the ZYN Flagship Varieties User Profile Study showed a consistent number of pouches used per day across flavors. Flavors had minimal impact on, and there was little variation in, the average number of minutes ZYN Products were used.

Table 1.3.1 Respondent Distribution of Flavor Varieties Most Frequently Used During the Prospective (b) (4) POU Study

Flavor Variety	N	%
Total	(b) (4)	
Cool Mint		
Wintergreen		
Spearmint		
Peppermint		
Cinnamon		
Coffee		

Table 1.3.2 Average Number of Pouches Used per Day During (b) (4) of Prospective POU Study

Flavor Variety	N	# Pouches
Cinnamon	(b) (4)	(b) (4)
Cool Mint		
Peppermint		
Spearmint		
Wintergreen		
Coffee		

Table 1.3.3 Average Number of Minutes ZYN Products Were Used During (b) (4) of Prospective POU Study

Flavor Variety	N	# Minutes
Spearmint	(b) (4)	(b) (4)
Wintergreen		
Peppermint		
Cool Mint		
Coffee		
Cinnamon		

1.3.3 Post-Hoc Strength Analysis: Addendum to Study Report (b) (4)

A post-hoc analysis was performed on the (b) (4), prospective ZYN POU Study (b) (4) to examine ZYN Product patterns of use and product switching by nicotine strength. More specifically, the ZYN Product patterns of use (average number of ZYN Product pouches used per day and average number of minutes ZYN Products were kept in the mouth) among ZYN Product users during the prospective observational period was analyzed by strength.

The distribution of nicotine strengths used by ZYN Product users during (b) (4) of the prospective study is shown in Table 1.3.4. The number of pouches used per day and average number of minutes ZYN Products were used are shown in Table 1.3.5 and Table 1.3.6, respectively. While the majority of users responded they exclusively used the original ZYN Flagship 6 mg Varieties, there was no significant difference in the number of pouches used per day or number of minutes ZYN Products were used between the original ZYN Flagship 3 mg and 6 mg Varieties.

Table 1.3.4 Respondent Distribution of Nicotine Strengths Used During (b) (4) of Prospective POU Study

Strength	N	%
Total	(b) (4)	(b) (4)
3 mg		
6 mg		
3 & 6 mg		

Table 1.3.5 Average Number of Pouches Used Per Day During (b) (4) of Prospective POU Study

Strength	N	# Pouches
3 mg	(b) (4)	(b) (4)
6 mg		
3 & 6 mg		

Table 1.3.6 Average Number of Minutes ZYN Products Were Used During (b) (4) of Prospective POU Study

Strength	N	# Minutes
3 mg	(b) (4)	
6 mg		
3 & 6 mg		

1.3.4 ZYN Flagship Varieties POU Study (b) (4) Conclusions

In summary, data show that ZYN Product users were current users of TNPs prior to initiating ZYN Product use. ZYN Product use was associated with reduced use of TNPs over time as daily smoking prevalence decreased from (b) (4) at the time of ZYN Product initiation to (b) (4) at the time of the retrospective data collection, and daily moist snuff use decreased from (b) (4) during the same period. During the (b) (4), prospective study period, exclusive ZYN Product use increased from (b) (4) demonstrating a continued transition in tobacco use pattern. Taken together, these results indicate that ZYN Product users are willing and able to substitute their cigarette and moist snuff use with ZYN Product use and thereby transition to a less harmful TNP. Furthermore, this evidence demonstrates that all populations understood the risks associated with use of the ZYN Products relative to use of other TNPs and no TNPs. Taken together, these data support that the original ZYN Flagship Varieties candidate products are APPH.

1.4 Recent Findings from NYTS – Absence of Appeal and Uptake of Nicotine Pouches Among Youth

While the current tobacco marketplace features numerous varieties (strengths, flavors) of nicotine pouches, including ZYN Products, recent NYTS data continue to demonstrate an absence of appeal and uptake of nicotine pouches among youth. NYTS has included questions regarding nicotine pouch use for two years (2021 and 2022, the two most recent NYTS data collections currently available). The overall use prevalence for U.S. youth based on surveys of middle and high school students was approximately 1% (2021: 0.76% [95% CI: 0.54% - 0.98%]; 2022: 1.06% [95% CI: 0.74% - 1.38%]; see also Gentzke et al. (2022), Park-Lee et al. (2022), Kramer et al. (2023), and Speciale et al. (2023)). Frequent pouch use (on 20 or more of the past 30 days) was rare in both 2021 and 2022 estimates; the 2021 estimate was 0.13% (95% CI: 0.06% - 0.20%) and the 2022 estimate was 0.27% (95% CI: 0.19% - 0.36%) of U.S. youth. Also notable is the observation that approximately 80% of past-30-day pouch users also report using other TNPs in the past 30 days (2021: 81.4% 95% CI: 74.3-88.6; 2022: 80.3% 95% CI: 71.3-89.2). In other words, only approximately 0.2% of U.S. youth report exclusive use of nicotine pouches, suggesting that these products are not attracting a class of youth users who would not otherwise use or experiment with TNPs. These results align with the findings from a recently published analysis of NYTS 2021 data that found nonusers of cigarettes or electronic nicotine delivery systems (ENDS) products to have significantly lower odds of using alternative nicotine products (Speciale et al., 2023).

These findings augment the results on nicotine pouch use among U.S. youth from other published literature as well. In addition to studies reporting on use prevalence through early 2022 described in the nicotine pouch literature review (Section 1.6), more recently published literature continues to support the finding that nicotine pouch uptake is low among this important unintended user group. For example, recent findings from the U.S. International Tobacco Control Policy Evaluation Project Youth Tobacco and Vaping Survey that showed similarly low levels of youth uptake of nicotine pouches, and that among those who ever used nicotine pouches, <1% tried nicotine pouches as their first tobacco product (Schneller, Felicione, Hammond, Goniewicz, & O'Connor, 2023). Further, estimates from the Altria Client Services UTUS, a repeated cross-sectional survey collecting data

on underage tobacco use on a quarterly basis, were similar to those based on NYTS data (Cheng et al., 2023). Nicotine pouch use estimates remained low throughout the May 2020 - August 2022 study period at less than 0.5% among youth (ages 13-17) and 1.7% or less among underage young adults (ages 18-20). While the authors appropriately recommend continued monitoring given moderate levels of product awareness, the lack of substantial uptake is noteworthy, particularly among underage young adults who are not well covered among school-based surveys like NYTS.

1.5 Population Modeling and Analysis

Swedish Match contracted (b) (4) to conduct a population health impact modeling study to estimate the public health impact of introducing the ZYN Product Line into the U.S. market. In addition, a manuscript based on the study report has been published (Lee, Fry, & Ljung, 2022). A summary of the population modeling study, as well as the full study report and published manuscript, are provided in the (b) (4).

The potential health impact of introducing the ZYN Product Line over the time period of 2000-2050 was investigated based on product-related mortality estimates and provides evidence, using conservative assumptions, that the introduction of the ZYN Product Line into the U.S. market would significantly reduce smoking-related mortality and morbidity. Over the 50 years, deaths at ages 35-84 due to product use are estimated to decrease by the equivalent of about 700,000 fewer deaths in the total U.S. population. Even under the pessimistic assumption that the reduction in excess mortality risk from use of products in the ZYN Product Line is 20% that from cigarette smoking rather than the 3.5% assumed in the main analysis, the estimated reduction in product-related deaths would only decline to 600,000 fewer deaths in the total U.S. population. Therefore, substantial public health benefits were maintained across the pessimistic scenarios included in the sensitivity analyses. These findings support the conclusion that the ZYN Product Line, including the candidate products, is APFH.

1.6 Nicotine Pouch Literature Review

As part of the PMTA Rule (FDA, 2021b), the FDA requires an applicant to conduct a literature search for several types of health risk information to provide "all relevant health risk data to determine whether permitting the marketing of the product would be appropriate for the protection of the public health." In the original PMTA, Swedish Match submitted systematic literature reviews of snus. At the time, the available literature on nicotine pouches was very limited. Swedish Match is now amending the PMTA to include this comprehensive literature review of nicotine pouches. Swedish Match commissioned (b) (4), to conduct an independent, comprehensive review of the peer-reviewed scientific, medical, and public health literature for oral nicotine pouch products. The literature review focused on three main areas including nonclinical – chemistry and toxicology; clinical individual health – clinical pharmacology, behavioral pharmacology, and individual health outcomes; and population health topics. The full details and most recently updated literature search findings can be found in the (b) (4).

The approach to this review was guided by several published recommendations, including the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019), the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher, Liberati, Tetzlaff, Altman, & Group, 2009), and standards set by the Agency for Healthcare Research and Quality ("AHRQ Methods for Effective Health Care," 2008). (b) (4) experts in several disciplines of public health and tobacco science collaborated

throughout the design, conduct, and reporting of the literature review, modifying the referenced guidance for systematic reviews for use in a nonsystematic, but nonetheless extremely comprehensive, literature review. This literature review also meets Section 1114.7(k)(2) requirements.

This comprehensive literature review on oral nicotine pouch products included literature related to population health topics, such as product perceptions, intentions to try, and likelihood of use; product appeal, reasons for use, and subjective effects among ever users of nicotine pouches; prevalence of nicotine pouch use; and changes in smoking and other tobacco use behaviors.

A detailed description of the methods used is available in th (b) (4)

References were identified from several sources: PubMed and Embase databases, abstracts and posters presented Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) and Society for Research on Nicotine & Tobacco meetings, study records with results in ClinicalTrials.gov, and the reference lists of relevant literature reviews. Subject matter experts provided citations for studies not otherwise identified. The information summarized herein pertains to the database searches performed on February 15, 2021 (initial search), with updates on January 4, 2022 (updated search 1) and January 3, 2023 (updated search 2).

Of the initial 763 unique results from the combined search strategies, 114 references were included after full-text review. Of the 114 included references, 57 (29 papers and 28 abstracts/posters/presentations) contained results relevant to population health. The complete results extracted from each included publication are available in the (b) (4)

For the purposes of this Amendment, we provide a brief summary of the population health section conclusions only; full results/findings are included in the TPMF.

1.6.1 Nicotine Pouch Population Health Literature Review Conclusions

In summary, available prevalence studies suggest that overall nicotine pouch use is low among youth and adults. This is not surprising, given that most of the currently available products have been on the market only a short time. Current or ever use prevalence among youth appears to be less than 2%, and current use may be less than 1%. Prevalence data is not yet available for the U.S. adult population as a whole, but it appears to be below 1% in U.S. current and former tobacco product users. International data also point to low population-level uptake. Nicotine pouch use seems to be most common among users of other tobacco products, including smokers and users of snus and smokeless tobacco, but more studies are needed to assess the true prevalence of nicotine pouch use and any trends in use over time.

Perceptions data indicate that both youth and adults are aware that there is some risk associated with nicotine pouch use, though that use was generally assessed to be lower than that of combustible tobacco products. Modified risk claims may decrease potential users' risk assessments, particularly among current tobacco product users. Among adults who tried a nicotine pouch, the majority of studies found that participants are interested in using a nicotine pouch to reduce or cease their tobacco use. The nicotine pouch may be more appealing to smokeless tobacco users and dual smokeless tobacco/cigarette users than to exclusive smokers. The likelihood of product uptake among adult never tobacco users and former tobacco users appears low, as reported by two large studies. Likelihood of product use among youth may be difficult to estimate due to lack of generalizability of the identified studies' findings and potential overestimation of the likelihood of product uptake by youth. Though limited, there is some evidence that nicotine pouches help smokers and smokeless tobacco users reduce

and quit tobacco use. Some results suggest that flavors may be an important factor to adult smokers when switching from cigarettes to a potentially less harmful novel oral pouch product. These results are in alignment with study results for products in the ZYN Product Line. Although the findings are promising, they should be interpreted with study quality in mind. Results from some of the included studies were reported in only poster or abstract form, and some studies have methodological weaknesses that include small sample sizes, the possibility of self-report bias, and failure to perform statistical testing and/or modeling. However, the recency of much of the data suggests that more thorough, peer-reviewed publications should be forthcoming.

Given that nonusers of tobacco products appear unlikely to become nicotine pouch users and that nicotine pouches appeal to current tobacco users, nicotine pouches like those in the ZYN Product Line may have a net positive impact on population health. Additionally, people who have tried nicotine pouches seem interested in using them to reduce or quit traditional tobacco product use, which further supports the ZYN Product Line as being APPH. It is expected that new evidence on these novel products should further support the aforementioned conclusions that nicotine pouches like those in the ZYN Product Line, including the original ZYN Flagship Varieties, have a net positive effect and are therefore APPH.

1.7 Integrated Conclusion

The diverse product portfolio of the ZYN Product Line, including the original ZYN Flagship Varieties is intended to meet the needs of (or “appeal to”) a variety of palates and preferences among current, adult tobacco users to help as many people as possible transition down the continuum of risk.

Swedish Match originally submitted the original ZYN Flagship Varieties PMTA on March 4, 2020.² Since then, additional studies and literature relevant to the candidate products have been collected and/or published. Therefore, Swedish Match proactively provides the most current scientific information to facilitate FDA review of the candidate products.

This Amendment provides new studies as well as expanded discussions of previously submitted studies to further contribute to the evidence regarding consumer behaviors and use patterns of the candidate products. Briefly, the overall findings in this Amendment further demonstrate the original ZYN Flagship Products are APPH, based on the following:

- **New Studies**
 - **ZYN Flagship Varieties User Profile Study** [REDACTED] (Section 1.1) findings suggest offering diverse flavor varieties and nicotine strengths are important components of user satisfaction, thus, allowing cigarette and/or other TNP users the opportunity to transition to a product lower on the continuum of risk.
 - **Recent findings from NYTS (Section 1.4)** continue to demonstrate an absence of appeal and uptake of nicotine pouches among youth, augmenting the results on nicotine pouch use among U.S. youth from other published literature.
 - The **population health impact modeling study of ZYN Products (Section 1.5)** indicates deaths at ages 35 to 84 due to product use are estimated to decrease by about 700,000 in the total U.S. population over the 50 years after introduction of the ZYN Product Line.

- An independent, **comprehensive review of the peer-reviewed scientific, medical, and public health literature for oral nicotine pouch products** (Section 1.6) is provided. The population health section of the literature review suggests youth and nonusers of tobacco products are unlikely to become nicotine pouch users, nicotine pouches appeal to current TNP users, and people who have tried nicotine pouches seem interested in using them to reduce or quit TNP use.
- **Expanded Discussion of Previously Submitted ZYN Product Studies**
 - **The ZYN Flagship Varieties LOU Study** (b) (4) (Section 1.2) demonstrates that never users and former users of TNPs do not find the original ZYN Flagship Varieties appealing and are unlikely to initiate or reinstate TNP use. Additionally, current TNP users have a low-to-moderate likelihood of use of the original ZYN Flagship Varieties and consumers generally have their own individual flavor preferences, supporting the need for a variety of reduced-risk products to move current TNP users down the continuum of risk.
 - **The ZYN Flagship Varieties POU Study** (b) (4) (Section 1.3) results demonstrate that, over time, a sizeable percentage of TNP users reduce their TNP use, completely switch to ZYN Products, or quit TNP use altogether.

Collectively, these studies demonstrate that the original ZYN Flagship Varieties provide population and individual level benefits by offering a variety of satisfying, reduced-risk options to current, adult TNP users, without appealing to never and former users of TNPs or youth. Considering the acceptability of flavored smokeless products among current, adult TNP users, FDA's historical precedence of MGOs for flavored traditional oral products, and the evidence of minimal youth appeal and uptake of such products, these findings further demonstrate the candidate products are APPH.

These important factors amount to population and individual level benefits that would be associated with ZYN Products' availability in the market. The information provided and referenced in this Amendment contains scientific evidence demonstrating that the benefits associated with ZYN Products' availability in the market would outweigh the known risks. Accordingly, a marketing order for the original ZYN Flagship Varieties would be APPH.

1.8 References

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