US Food and Drug Administration

Tobacco Products Scientific Advisory Committee (TPSAC)

22nd Century Group Inc. Briefing Materials

VLN® Reduced Nicotine Cigarettes

MR0000159 and MR0000160

VLN® King Box and VLN® Menthol King Box

February 14th, 2020

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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1 INTRODUCTION AND BACKGROUND

On May 13, 2019, 22nd Century Group, Inc. ("XXII" or the "Company") submitted Modified Risk Tobacco Product Applications ("MRTPAs") to the U.S. Food and Drug Administration ("FDA" or the "Agency") under Section 911(g) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), as amended by the Family Smoking Prevention and Tobacco Control Act ("TCA"), requesting Exposure Modification Orders for two versions of reduced nicotine content cigarettes; VLN® King Box (MR0000159) and VLN® Menthol King Box (MR0000160) (together, the "VLN® MRTPAs"). The VLN® MRTPAs seek orders permitting XXII to include the following claims in the labeling and advertising for the tobacco products:

1) Claim #1 : "95% less nicotine"

2) Claim #2 : "Helps reduce your nicotine consumption"

3) Claim #3 : "…. greatly reduces your nicotine consumption"

XXII believes that reduced nicotine consumption by current adult consumers of conventional tobacco products results in demonstrable public health benefits, both to individual consumers of combusted tobacco products and to the population as a whole. FDA agrees: on December 17, 2019, FDA issued marketed orders permitting commercialization of these same tobacco products pursuant to Premarket Tobacco Product Applications filed by the Company (the "VLN PMTAs"), concluding that marketing authorization was "appropriate for the protection of the public health" under the applicable statutory criteria. FDA reached this determination because, among other reasons, smokers who switch to the Company's proprietary very low nicotine content ("VLNC") cigarettes will "reduce their exposure to nicotine and a range of non-nicotine HPHCs, may smoke fewer [cigarettes per day], may reduce their nicotine dependence levels, and increase their quit attempts" compared to those who continue to smoke conventional cigarettes. (TPL Report, Page 8).

While XXII believes that the potential health benefits of switching to VLN® cigarettes are abundantly clear, it is essential for this proceeding to note that the Company is not seeking an MRTPA order that would permit it to claim that use of the products will in fact reduce the risk of tobacco-related diseases to individual users. Rather, XXII is seeking permission to only make the

limited claims above related to reduced nicotine consumption. Indeed, the Company includes prominent warnings on the front label of the product stating that the VLN® products are not safer than conventional cigarettes (i.e., "Less nicotine does NOT mean safer. All cigarettes can cause disease and death"). Use of such disclaimers is intended to limit appeal beyond the consumers XXII intends to reach: current adult smokers who are seeking to reduce their consumption of nicotine.

The fact that XXII is not seeking permission to make "risk reduction" claims for its VLN® products makes this application very different from the MRTPAs that TPSAC has considered in prior hearings. In those proceedings, TPSAC reviewed such "risk reduction" claims and the associated clinical and epidemiological evidence supporting the applicants' belief that such claims would result in significant reductions in harm and the risk of tobacco-related disease to individual users of tobacco. Here, FDA has already confirmed that potential public health benefits would accrue from reduced consumption of nicotine by current users of tobacco products, and TPSAC's mandate is therefore limited to consideration of XXII's proposed communication of this message in a manner that incentivizes current smokers to switch to the VLN® products while not increasing the likelihood that current non-users of tobacco will initiate smoking through purchase of the products. The Company believes the results of extensive consumer perception research included in the MRTPAs proves that to be the case, and XXII summarizes those findings herein.

Ultimately, the Company believes that the data and information included in the VLN® MRTPAs, along with key findings from FDA's review of the VLN® PMTAs, make it appropriate for FDA to issue exposure modification orders under §911(g)(2) of the FD&C Act ("Exposure Modification Orders") permitting advertising bearing the claims proposed by the Company.

1.1 VLN®: A Product Developed in Partnership with Public Health

Today, it is well understood that nicotine is the primary driver of tobacco use and smoking behavior. The chronic and compulsive consumption of tobacco smoke for nicotine leads to exposure to numerous carcinogens and other toxicants, resulting in almost half a million deaths in the U.S. each year; 7 million globally. (CDC, 2019).

In 1994, Drs. Benowitz and Henningfield proposed reducing nicotine levels of all cigarettes, (*see* Benowitz and Henningfield, 1994) and in 1998, XXII's VLNC tobacco was developed as a response to this and other such proposals. Since its introduction, VLNC tobacco has been used in many research and lawfully-marketed cigarettes under different trade names, including X-22, Xodus, Magic, MAGIC 0, MAGIC 2, Quest®, SPECTRUM®, PARE®, VLN® King and VLN® Menthol King.

Following passage of the TCA, XXII sought opportunities to work with FDA in developing and potentially commercializing VLNC cigarettes as a viable method for reducing smokers' nicotine consumption. For example, in 2011, XXII developed the X-22 cigarette as an investigational new "drug" product intended to facilitate smoking cessation. XXII conducted a clinical study of X-22 cigarettes under an investigational new drug application authorized by FDA (IND#103589). The study revealed no meaningful difference between X-22 and the active control in abstinence rates three months after the quit date. Subsequently XXII halted the development of X-22 to evaluate other VLNC cigarettes and focus on the role of such products in non-drug (*i.e.,* non-cessation) applications, such as reducing nicotine exposure. In 2011, XXII also developed the SPECTRUM® line of research cigarettes in collaboration with independent researchers and officials from FDA, the National Institute on Drug Abuse, the National Cancer Institute and the Centers for Disease Control and Prevention. The main SPECTRUM® product line consisted of a series of cigarette styles that varied in nicotine content – from very low (~0.4 mg/g tobacco) to relatively high contents and yields. The VLNC versions of SPECTRUM® cigarettes, referred to as NRC102 and NCR103, are the same products as VLN® King Box (MR0000159) and VLN® Menthol King Box (MR0000160), respectively.

In 2015, XXII submitted both a PMTA and MRTPA for its PARE® brand of cigarettes, a consumer version of the NRC102 and NRC103 very low nicotine content products. After receiving constructive feedback from FDA on the applications, including feedback regarding the design of consumer perception studies required to support FDA's issuance of modified exposure orders, XXII voluntarily withdrew these applications to conduct additional scientific and consumer studies of its VLNC cigarette products. On December 4, 2018, XXII submitted the VLN® PMTAs to FDA, which the Agency subsequently authorized on December 17, 2019. In the PMTA scientific review report from FDA's Technical Project Lead (the "TPL Report"), FDA concluded that permitting

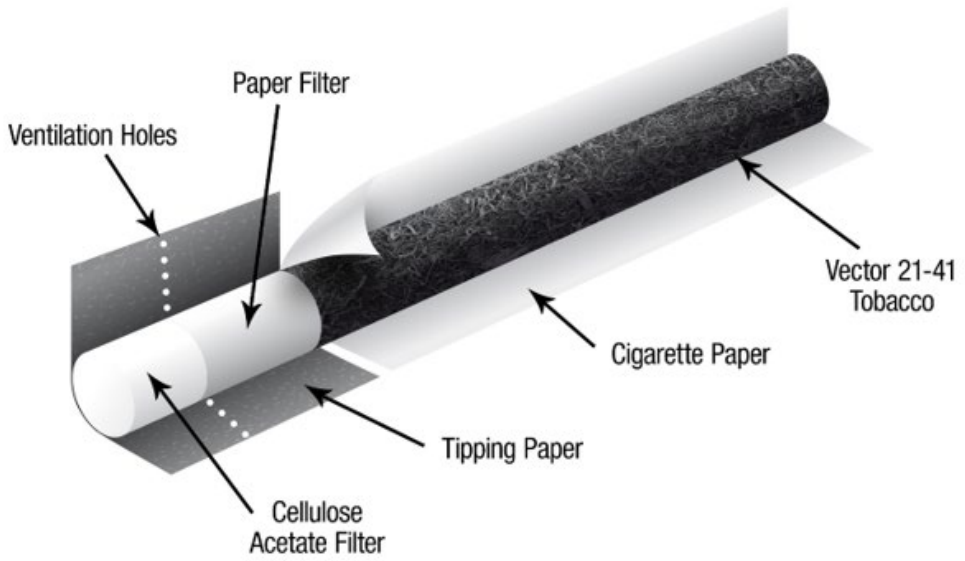
the marketing of the same VLNC cigarettes described in these applications under the brand name Moonlight® would be appropriate for the protection of the public health, as described in §910(c)(4) of the FD&C Act. (TPL Report, Page 10).

Finally, in May 2019, following more than 20 years of public health research evaluating the concept of a VLNC cigarette (including XXII's SPECTRUM® products), hundreds of publications and presentations, including analyses by FDA and the World Health Organization, (*see* Berman & Glasser, 2019) and almost 10 years of experience with FDA, XXII submitted the MRTPAs for the VLN® brand cigarette varieties that are the subject of this briefing document, requesting Exposure Modification Orders developed to enable smokers to reduce their nicotine consumption.

1.2 VLN® King and VLN® King Menthol Product Description and Nicotine Content

XXII manufactures VLN® cigarettes in the same manner as conventional cigarettes, using materials, ingredients, and processes well-established in the cigarette industry. As a result, the product appears to be a conventional cigarette and is intended to be consumed in the same way as a conventional cigarette. Indeed, the only difference between VLN® and conventional cigarettes is that VLN® cigarettes contain VLNC tobacco.

Figure 1 Diagram of VLN® Cigarette.



VLN® King and VLN® Menthol King cigarettes are the same as the NRC102 and NRC103 SPECTRUM® VLNC research cigarettes. The VLN® cigarettes are also the same as the PARE® cigarettes that were the subject of the previous applications referenced above. The only difference between each respective regular or menthol version of the VLN®, PARE® and SPECTRUM® NRC102/NRC103 brand style is the name of the product and the printing of the brand name on the tipping paper. Studies have been conducted on VLN® and SPECTRUM® cigarettes measuring smoke chemistry, abuse liability, smoking behavior, and topography. The results of the studies with VLN® cigarettes were consistent with those published for SPECTRUM® NRC102/NRC103 cigarettes.

1.3 Proposed VLN® Modified Exposure Claims

The Company has developed its VLNC tobacco and VLN® cigarettes for the express purpose of helping adult cigarette smokers to reduce their exposure to nicotine. The nicotine level in XXII's proprietary VLNC cigarettes is at least 95% less when compared to the top 100 cigarette brands in the U.S. marketplace (*see* Appendix I, below). In the TPL Report, FDA agreed with this conclusion noting that "[XXII's] statement that VLN® cigarettes statement have 95% less nicotine when compared to the top 100 U.S. cigarette brands and top 6 U.S. market leading king-sized cigarette brands appear[s] to be accurate," and that "the reported 97% decrease in nicotine deliveries under the [Canadian Intense] smoking regime supports [XXII's] '95% Less Nicotine' statement for its products." (TPL Report, pages 19 and 27). Despite this reduced nicotine content in the tobacco and in the smoke, the Company acknowledges that VLN® cigarettes have the same toxicological risks as conventional cigarettes and that any potential health benefits of using the products will result from the myriad incidental benefits that accrue from decreased nicotine exposure. To be clear, the Company agrees with FDA that there are no safe tobacco products and those who do not use tobacco products should not start.

The VLN® MRTPAs are therefore limited to a request that FDA issue Exposure Modification Orders allowing the Company to make the following three truthful and not misleading claims:

1) Claim #1: "95% less nicotine"

2) Claim #2: "Helps reduce your nicotine consumption"

3) Claim #3: "…. greatly reduces your nicotine consumption"

1.4 Claim Development for VLN®

Building on the feedback XXII received from FDA on the PARE® MRTPAs, XXII conducted consumer perception studies to develop truthful, non-misleading statements that can be understood by consumers and are based on valid scientific evidence. Importantly, VLN® cigarette products and the associated claims have been developed to address current, adult smokers with an interest in reducing their nicotine consumption.

XXII sought to create labels, labeling and advertising that maximize adult smokers' interest in the product as a substitute for conventional cigarettes, while reinforcing the idea that such users would be better off quitting smoking entirely. Further, the Company sought to minimize interest in the product among adult never smokers, former smokers and youth. Finally, the Company crafted the claims in a manner intended to avoid a reduction in the intention to quit among adult smokers who have the intention to quit conventional cigarettes.

XXII has closely followed FDA's health and regulatory policy, and the Company's interactions with FDA over the past decade have supported the evaluation of consumer perceptions and the design labeling and claims that the Company believes are consistent with FDA's policy goals. For example, XXII incorporated FDA feedback from prior MRTPA and PMTA submissions to make meaningful additions to the consumer perception research program, such as:

1) exposing respondents to three-dimensional images along with flat images, and thereby offering participants a more realistic experience with test packaging through digital models;

2) adding a second measure of "intent to use"' to subject questionnaires to evaluate any change in the original intent responses;

3) adding a direct comparison of the test concept to one of the four comparator categories on perceived health risk; and

4) collecting a large oversample of never smokers of legal age-to age 25 ("LA-25") to provide additional data of a proxy measure for youth and to ensure precision in the data.

The final statements in the proposed claims that are the subject of the VLN® MRTPAs represent the product of learning and refinement over the course of multiple studies, including four iterative phases of a qualitative study and a further quantitative study, as well as a considerable body of scientific literature developed by other researchers.

The perception of the product packaging and claims are discussed in detail in Section 3, below.

2 MODIFIED EXPOSURE ORDER STATUTORY REQUIREMENTS

XXII's MRTPAs for VLN® cigarettes will require TPSAC to engage in a more limited inquiry as compared to the prior hearings it conducted in connection with other applicants' MRTPAs. Specifically, unlike those prior filings, the Company is requesting that FDA issue "exposure modification" orders under Section 911(g)(2) of the FD&C Act, which would be limited to claims related to the nicotine content of the tobacco products that are the subject of the MRTP application. XXII is not requesting that FDA authorize "risk modification" claims under Section 911(g)(1) of the FD&C Act – that is, claims that the products present a lower risk of tobacco related disease or are less harmful than other commercially marketed tobacco products (a "Risk Modification Order"). As such, XXII's MRTPAs are not required to demonstrate that the VLN® cigarettes will significantly reduce harm or reduce the risk of tobacco-related disease to individual tobacco users, as would otherwise be required if XXII sought to make risk modification claims. Rather, under the FD&C Act, XXII must show that:

1) §911(g)(2)(A)(i): the exposure modification order would be appropriate to promote the public health;

2) §911(g)(2)(A)(ii): the label, labeling, and advertising for the product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;

3) §911(g)(2)(A)(iii): scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under Section 911(g)(1) of the FD&C Act (i.e., a risk modification order);

4) §911(g)(2)(A)(iv): the scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies;

5) §911(g)(2)(B)(i): the magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;

6) §911(g)(2)(B)(ii): the product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;

7) §911(g)(2)(B)(iii): testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and

8) §911(g)(2)(B)(iv): issuance of the exposure modification order is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

While the findings that FDA needs to reach in order to grant an Exposure Modification Order are numerous, there is no question that the standard for review is, and that Congress intended it to be, less burdensome than the extensive findings required to support a Risk Modification Order. This distinction is important, because the forthcoming TPSAC meeting represents the first time that TPSAC will be asked to evaluate MRTPAs that are limited to an exposure modification claim. Indeed, all of the MRTPA previously reviewed by TPSAC have obligated the Committee to consider voluminous clinical and epidemiological evidence regarding the tobacco product's relative harm and its effects on specific disease endpoints. In contrast, XXII's proposed labeling clearly and unequivocally states that VLN® cigarettes are no safer than conventional cigarettes.

Because FDA – and by extension, TPSAC – is not required to make any findings with respect to whether VLN® cigarettes will, in fact, reduce harm or the risk of tobacco-related disease on

individual users, certain topics that have featured prominently during prior TPSAC meetings will not be relevant during the forthcoming TPSAC meeting, such as the evaluation of clinical and epidemiological evidence of disease risks. Moreover, although Section 911(g)(2) of the FD&C Act does require TPSAC and FDA to determine that a reduction in morbidity and mortality is "reasonably likely" if the MRTP orders are issued, TPSAC need only refer to the conclusions reached by FDA contained in the TPL Report for the VLN® PMTAs. Among other findings, the Agency determined that:

> "…[e]vidence from clinical studies may indicate that associated noncancer hazards and cancer risks could be lower compared to marketed cigarettes…" and that "toxicological impacts may be proportionately decreased if users were to switch, due to a reduction in [cigarettes per day]...." (TPL Report, page 7).

Further, FDA concluded in its approval of XXII's PMTA that, with respect to potential dual users of XXII's product and conventional cigarettes, "noncancer hazards and cancer risks…are also likely to be similar or lower" and that:

> "smokers who choose to switch to [VLN® cigarettes] would experience the benefit of significantly reducing their overall exposure to nicotine, potentially reducing their overall smoking, and subsequently, their exposure to non-nicotine HPHCs." (TPL Report, page 10).

With this important context in mind, XXII believes that the MRTPAs that it has presented to FDA clearly meet the requirements for an exposure modification order as set forth in Section 911(g)(2) of the FD&C Act. The Company details the basis for this conclusion below.

3 THE VLN® MRTPAS MEET THE CRITERIA FOR FDA'S ISSUANCE OF AN EXPOSURE MODIFICATION ORDER UNDER 911(g)(2)

3.1 §911(g)(2)(A)(i): FDA's issuance of an exposure modification orders for VLN® cigarettes would be appropriate to promote the public health

Following FDA's rigorous review of the same product in the VLN® PMTAs, the Agency agreed with the Company's claim that VLN® cigarettes contain 95% less nicotine than other conventional cigarettes on the U.S. market. (TPL Report, page 19).

Moreover, both the Company and independent researchers have confirmed the benefits of such a substantial reduction in nicotine across a remarkable number of clinical studies evaluating VLNC cigarettes. (Berman & Glasser, 2019). Taking these studies into consideration during its review of the VLN® PMTAs, FDA concluded that "[p]ermitting the marketing of [XXII's VLN® cigarettes] would be appropriate for the protection of the public health, as described in §910(c)(4) of the FD&C Act." (TPL Report, page 69). The Company agrees with the conclusions contained in the TPL report and notes that the same conclusions apply to the VLN® MRTPAs. Indeed, XXII believes that truthful and non-misleading exposure modification claims are needed in order for adult smokers to understand how VLN® cigarettes differ from conventional cigarettes and thereby understand both the benefits and risks of VLN® King and VLN® Menthol King cigarettes.

3.2 §911(g)(2)(A)(ii): The label for VLN® cigarettes is limited to an explicit or implicit representation that the product contains a reduced level of nicotine

XXII has designed the proposed packaging to conform to the statutory limitations set forth in §911(g)(2)(A)(ii) of the FD&C Act. If the VLN® MRTPAs are authorized, both of the VLN® products (King and Menthol King) will carry the primary claim of "95% Less Nicotine" on the front and back of the product pack. The claim "Helps reduce your nicotine consumption" will appear on the front and the back of the pack under the "95% Less Nicotine" statement. A similar claim on the back of the pack would state:

VLN® smells, burns, and tastes
like a conventional cigarette,
but greatly reduces your
nicotine consumption.

VLN® cigarettes would be sold in typical cigarette packaging, as seen below.

Figure 2: 3-D Image of Representative VLN® Pack

As indicated above, the proposed packaging does not employ claims, colors or features that are commonly considered to be associated with marketing to a specific gender or that might risk appealing to youth; the packaging and trade dress are designed to be orthodox in their conception and presentation. Importantly, the proposed packaging bears a prominent and unequivocal warning on the front of the label stating that VLN® cigarettes are not safer than conventional cigarettes. This warning is intended to minimize any potential appeal beyond the intended consumer demographic (i.e., current adult smokers who wish to reduce their nicotine consumption).

In addition, all packs of VLN® cigarettes will bear the required health warnings mandated by the Federal Cigarette Labeling and Advertising Act of 1966. Because the claims added to the proposed packaging are limited to explicit representations regarding the content of nicotine, the packaging meets the statutory requirements set forth in §911(g)(2)(A)(ii) of the FD&C Act.

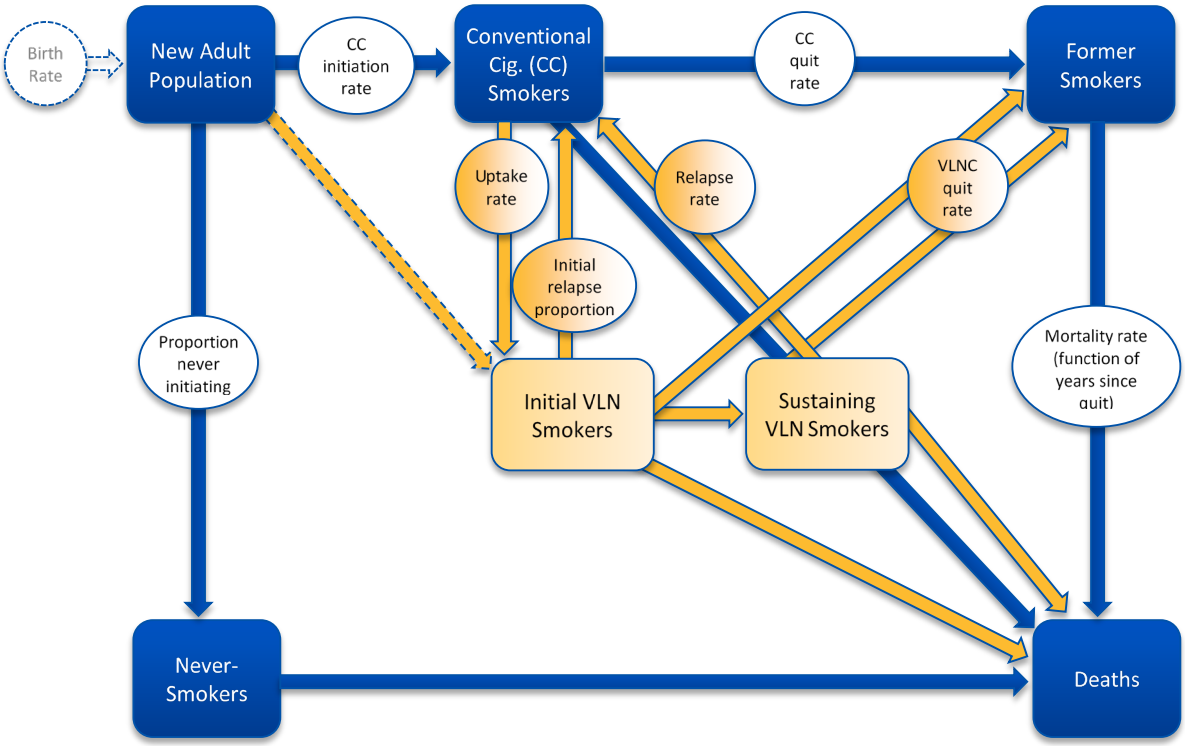
3.3 §911(g)(2)(A)(iii): scientific evidence is not available to support a risk modification claim for VLN® cigarettes, and cannot be made available without conducting long-term epidemiological studies

XXII is not seeking a risk modification claim for VLN® cigarettes at this time. Although FDA recently authorized the Company to market the same VLNC cigarettes described in these MRTPAs under the brand name Moonlight®, the Company has not yet introduced these products into the U.S. market. Moreover, there are no commercially available cigarettes in the U.S. market either utilizing XXII's technology or containing the very low levels of nicotine found in VLN® cigarettes. Accordingly, the type of long-term data arising from the use of VLN® cigarettes that would be required to support a Risk Modification Order are not available and will not be available on a premarket basis. As such, VLN® cigarettes meet the prerequisite set forth in §911(g)(2)(A)(iii) for seeking an Exposure Modification Order.

3.4 §911(g)(2)(A)(iv): the scientific evidence that is available for VLN® cigarettes suggest that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies

Studies conducted by both XXII and independent researchers suggest that VLN® cigarettes may lead to substantial reductions in morbidity and mortality. FDA itself agreed with this view in the TPL Report, noting that "[d]ata from the literature suggest that those who do switch to VLNC cigarettes reduce their exposure to nicotine and a range of non-nicotine [harmful and potentially harmful constituents], may smoke fewer [cigarettes per day], may reduce their nicotine dependence levels, and increase their quit attempts compared to those who continue to smoke [conventional cigarettes]." (TPL Report, Page 8). Any of these outcomes would reduce morbidity and mortality of individual smokers, but when applied to the population as a whole, such outcomes suggest broad and substantial reductions. Indeed, in developing the MRTPAs, XXII modeled the effect of the VLN® product on the population as a whole starting with product introduction in 2020.

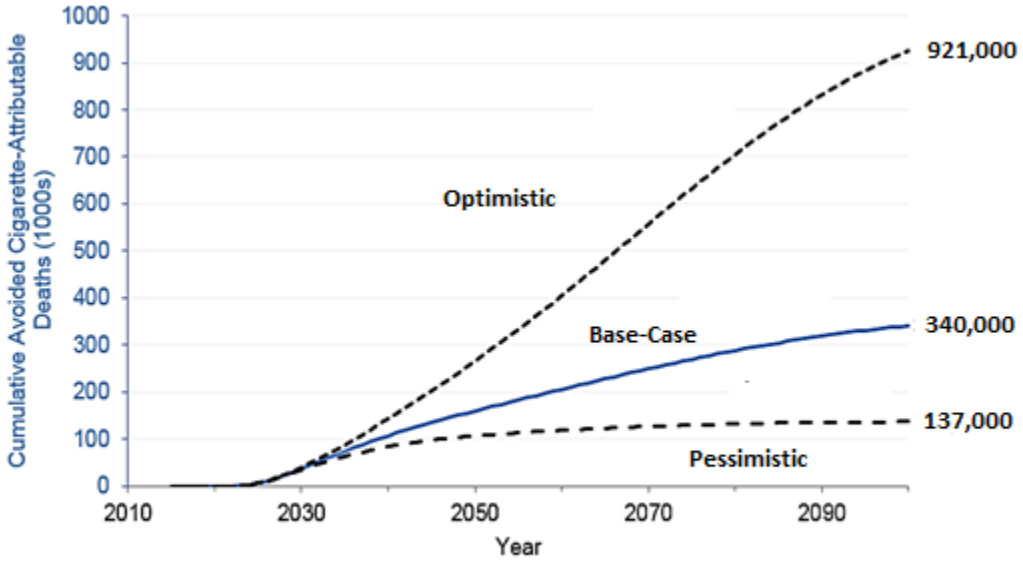
Figure 3: Diagram of Population Model.



The model simulates the whole U.S. adult population categorized by age, sex, and current/former smoking state from 2015 to 2100. For each set of inputs, the model predicts the long-term effects of VLN® cigarettes by comparing one simulation without their introduction to the market (blue sub-diagram above) and one in which they are introduced in 2020 and then gradually approach 25% market penetration. The mortality impact of VLN® cigarettes is determined by the differences in total life-years and total cigarette-attributable deaths between the two simulations. This model assumes that the availability of VLN® cigarettes will not affect total smoking initiation, such that any mortality reduction would result solely from VLN® users' increased quit rates and reduced cigarettes per day relative to conventional smokers.

This model analyzes the potential effects of VLN® cigarettes under base, optimistic, and pessimistic cases. The optimistic case raises the relative quit rate for VLN® users and lowers the relapse rate from VLN® to conventional cigarettes; the pessimistic case does the opposite. Cumulative avoided cigarette-attributable deaths for each case are shown below.

Figure 4: Modeled Scenario of Avoided Cigarette-attributable Deaths.



In the base case, XXII's model predicts that introducing VLN® cigarettes will avoid about 340,000 smoking-attributable deaths and add about 8.05 million life-years by the year 2100 (cumulative). In the optimistic case, the model predicts almost one million avoided smoking-attributable deaths and almost 19 million life-years gained. Sensitivity analysis revealed the increased quit rate of VLN® users as the primary driver of mortality reduction.

The model further suggests that younger adults will experience the greatest long-term benefits due to their longer opportunity to switch to VLN® cigarettes, and ultimately, transition from smoking conventional cigarettes entirely.

In recent related work, a study led by Dr. Ben Apelberg modeled the effect of a potential reduced nicotine product standard in the U.S. (Apelberg, 2018). The model compared a baseline scenario (assuming that cigarette smoking will continue to decline based on recent trends in smoking initiation and cessation and from a median smoking prevalence of 12.8%) with a policy scenario in which a product standard is put in place in 2020 to lower levels of nicotine to minimally or non-addictive levels in cigarettes and other combustible tobacco products that are highly likely to serve as substitutes for traditional cigarettes (i.e., roll-your-own tobacco, pipe tobacco, non-premium cigars). In the policy scenario, the study estimated that only about 1.4 percent of the U.S. adult

population would smoke cigarettes by 2100, in part because more than 33 million people would avoid smoking initiation. (Apelberg, 2018). A similar policy scenario was also examined in XXII's model assuming a mandated reduction in cigarette nicotine content to minimally addictive levels in the year 2020. In this scenario, XXII's model predicts about 8.2 million avoided smoking-attributable deaths and 150 million life-years gained by the year 2100, a result substantially similar to Apelberg's base-case (8.5 million and 134 million, respectively). Each of these models supports the findings from the studies included in the VLN® MRTPAs, which collectively suggest that VLN® cigarettes may lead to substantial reductions in morbidity and mortality. As such, VLN® cigarettes meet the standard set forth in §911(g)(2)(A)(iv) for seeking an Exposure Modification Order.

3.5 §911(g)(2)(B)(i): the magnitude of overall reductions in exposure to nicotine is substantial, which is a harmful substance, and VLN® cigarettes, as actually used, will expose consumers to the specified reduced level of nicotine

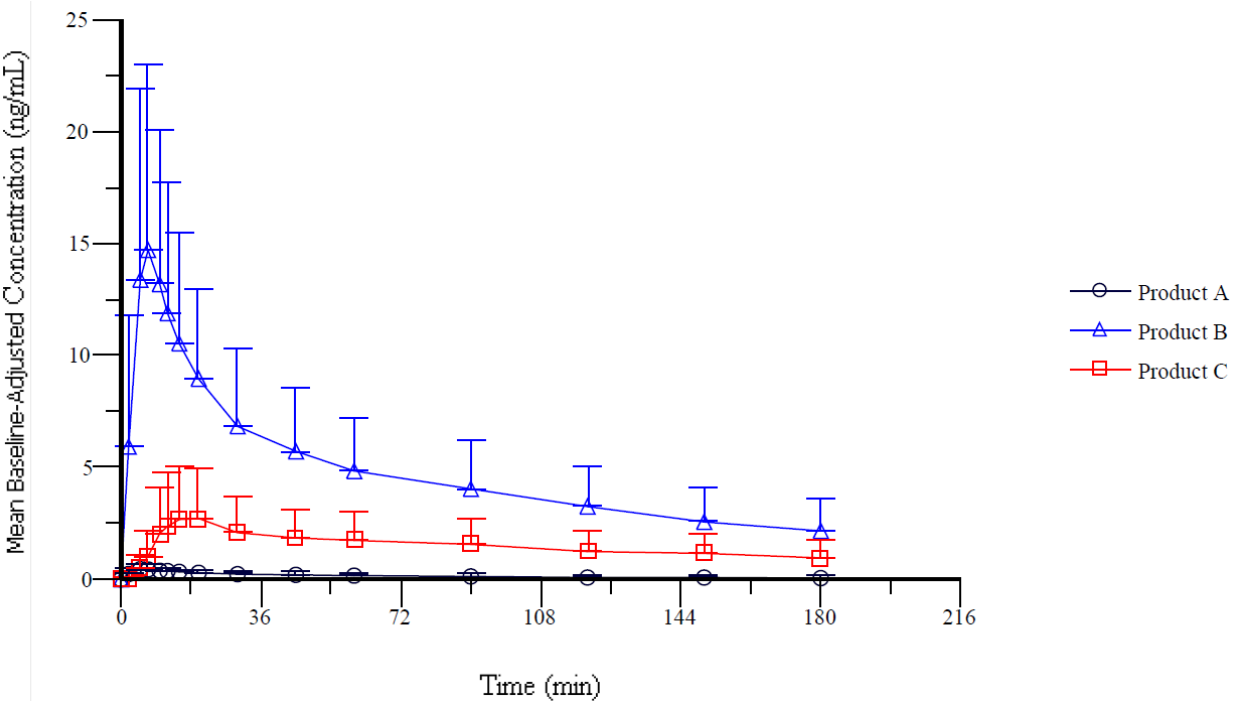
VLN® cigarettes expose smokers to substantially less nicotine than conventional cigarettes. Indeed, in the TPL Report, FDA concurred with XXII's finding that VLN® cigarettes contain at least 95% less nicotine when compared to 100 top-selling cigarette brands in the U.S. (TPL Report, page 19). Moreover, the Agency found that smokers who switch to VLN® cigarettes will likely experience reduced exposure to nicotine, even if such users do not decrease their daily cigarette consumption. (TPL Report, Page 8).

It is important to clarify that nicotine is a "harmful substance" within the meaning of §911(g)(2)(B)(i) of the FD&C Act, as evidenced by FDA's discussion of nicotine in proposed rules and guidance documents. For example, in evaluating a proposed regulatory standard that, if enacted, would require a reduction in the levels of nicotine in cigarettes to minimally or non-addictive levels, FDA stated that "it is the presence of nicotine that causes youth, young adults, and adult users to become addicted to, and to sustain, tobacco use," and that "[o]nce tobacco users become addicted to nicotine, they require nicotine to avoid certain withdrawal symptoms. In the process of obtaining nicotine, users of combusted tobacco products are exposed to an array of toxicants in tobacco and tobacco smoke that lead to a substantially increased risk of morbidity and mortality." (83 Fed. Reg. 11818, March 16, 2018). Similarly, in draft guidance FDA has stated

that it considers the tobacco dependence caused by nicotine "to be a serious and life-threatening condition." (NRT Draft Guidance, 2019). The Agency has also classified nicotine as a Harmful and Potentially Harmful Constituent ("HPHC") in tobacco products and tobacco smoke, citing both its addictiveness and reproductive and developmental toxicity. (77 Fed. Reg. 20034, April 3, 2012).

Furthermore, as noted above, data from clinical studies show that as actually used, VLN® cigarettes will expose users to reduced levels of nicotine. For example, in a study that evaluated the abuse liability of VLN® King cigarettes relative to participants' own-brand cigarettes and nicotine gum, XXII observed that blood plasma nicotine levels following VLN® cigarette use were significantly reduced from the blood plasma nicotine levels of those participants using either their usual brand of cigarette or those using 4 mg nicotine gum, as shown below.

Figure 5: Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration (ng/mL) after *ad libitum* use of VLN® King, Usual Brand and 4 mg Nicotine Gum



(Product A = VLN® King, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

The time to maximum nicotine concentration (tmax) in plasma was essentially the same for VLN® King cigarettes and for respondents' usual brand; this result was expected since the route of

exposure was the same (i.e., cigarette). Similar pharmacokinetic results were obtained with VLN® Menthol Kings. In the TPL Report, the Agency stated that the "pharmacokinetic (PK) profile of VLN® cigarettes indicates a lower abuse liability than the applicant's usual brand-normal nicotine content . . . cigarette comparator," a finding that reflects the lower nicotine exposure of VLN® cigarettes. (TPL Report, Page 7).

3.6 §911(g)(2)(B)(ii): VLN® cigarettes, as actually used by consumers, will not expose them to meaningfully higher levels of other harmful substances compared to conventional cigarettes, any such increases are minimal and the reasonably likely overall impact of use of VLN® cigarettes remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;

The data and studies referenced in the VLN® MRTPAs show that users of VLN® cigarettes will not be exposed to meaningfully higher levels of HPHCs when compared to conventional cigarettes.

In connection with the VLN® PMTAs, FDA evaluated the toxicological profile of VLN® cigarettes and the potential resulting impact on individual morbidity and mortality and concluded:

> "After consideration of all the toxicological data presented, the overall toxicological risks of VLN® cigarettes are likely similar to those associated with use of the six comparator products that represent a significant portion of the cigarette market. However, the potential for a relative benefit compared to [normal nicotine content] cigarettes exists for smokers who switch completely to VLN® cigarettes, then reduce cigarette use, and eventually totally quit." (TPL Report, Page 34).

In addition, independent studies of VLNC cigarettes show that daily smokers gradually reduced their cigarette consumption by as much as 50% over 20 weeks of use. (*see* Hatsukami, 2018; Donny, 2015). Such studies also showed that non-daily smokers reduced their cigarette consumption after extended use of VLNC cigarettes. (Shiffman, 2018). To the extent that use of VLN® cigarettes will result in reduced cigarette consumption, such reductions would reasonably be expected to lead to substantial and measurable reductions in morbidity and mortality over time.

XXII agrees with FDA's view that the "[o]verall toxicant-associated noncancer hazards and cancer risks due to use of VLN® cigarettes are likely similar to the . . . six comparator [normal nicotine content] cigarettes that represent approximately 25% of the cigarette market, assuming that the VLN® cigarettes will be used in the same way as the comparators." (TPL Report, Page 7). Although the Company reiterates that VLN® cigarettes are not safer than conventional cigarettes, the toxicology and use information provided in the VLN® MRTPAs confirms that VLN® cigarettes do not present any material additional toxicological risks.

3.7 §911(g)(2)(B)(iii): Testing of actual consumer perception shows that, as XXII proposes to label and market VLN® cigarettes, consumers will not be misled into believing that VLN® cigarettes are or have been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products;

The results of the consumer perception testing included in the VLN® MRTPAs show that the Company's proposed risk modification claims will not mislead consumers into believing that VLN® cigarettes are less harmful than other tobacco products, such as conventional cigarettes, e-cigarettes, moist snuff or nicotine replacement therapies ("NRTs"), or that VLN® cigarettes present less of a risk of disease when compared to such tobacco products. As discussed in further detail below, these studies, taken together, satisfy the standard set forth in §911(g)(2)(B)(iii) of the FD&C Act.

3.7.1 *Design of VLN® consumer perception studies.*

As part of the MRTPA development program, qualitative perception studies, including focus groups and in-depth interviews, were conducted to evaluate consumer views regarding reduced risk and reduced exposure statements. The statements were modified and refined over the course of the four different studies. The last study evaluated only reduced exposure statements. The primary objectives of this research included:

1) Evaluating consumer perception of and understanding surrounding proposed advertising and pack messaging for Brand A (PARE® / VLN®).

2) Understanding perceptions of risk and communication of that risk through the statements on the pack.

All pack messages were evaluated with standard U.S. Surgeon General warnings for cigarettes.

Evaluation of the final statements that have been included on the proposed packaging for VLN® cigarettes indicated that consumers did not interpret the VLN® packaging or the VLN® exposure modification claims to mean that the VLN® cigarettes were safer than conventional cigarettes.

Although smokers did not consider VLN® cigarettes to be safer than conventional cigarettes, smokers did express confusion about the role of nicotine in smoking-related disease. Accordingly, in developing the packaging for submission in the VLN® MRTPAs, XXII added an additional prominent statement to each pack to reinforce the concept that VLN® cigarettes are not safer than conventional cigarettes. The inclusion of "disease and death" on the front of pack in the bottom half was the most preferred alternative. Although some participants felt that "death" was a more blunt term than other options, they believed the term nonetheless clearly communicated the facts in an "honest manner."

Figure 6: Supplemental Proposed Statement on VLN® to Communicate Risk of Cigarette Consumption.

Nicotine is addictive. Less nicotine does **NOT** mean safer. All cigarettes can cause disease and death.

This statement is also presented in Figure 2, above.

In light of these findings, the Company incorporated an additional statement in the VLN® packaging stating that "Less nicotine does NOT mean safer. All cigarettes can cause death and disease" to address any potential confusion regarding the role of nicotine and to more clearly meet the statutory requirement in §911(g)(2)(A)(ii) of the FD&C Act that the label be limited to representations regarding the reduced substance.

The purpose of the quantitative consumer perception study was to measure responses to versions of the VLN® pack label and messaging within populations of: (i) adult smokers with an intention to quit, (ii) adult smokers without any intention to quit, (iii) adult former smokers, and (iv) adult never smokers. There were approximately 3,500 participants per control condition and slightly more than 7,000 participants for each experimental condition. Former smokers and current smokers were further divided based on cessation recency and intention to quit within the next six months, respectively. Other subsets of current smokers included light smokers (less than 10 cigarettes per day) and heavy smokers (10+ cigarettes per day) as well as menthol versus non-menthol preferences. In addition, an oversample of young adult never smokers (e.g., LA-25) was used to enable the collection of sufficient data to describe responses within this group independently, and to act as a proxy for youth. Legal age was defined as the minimum age for tobacco purchase as determined by each participant's U.S. state of residence.

Specifically, the study aimed to assess risk perceptions and intent to use for VLN®, Marlboro Gold and four comparator categories: Conventional Cigarettes (CC) i.e. normal nicotine content cigarettes, NRTs, electronic cigarettes (e-cigs), and moist snuff. Subjects were randomly assigned a concept following a least-fill method to ensure representative distribution within each concept across cigarette usage and demographic criteria.

Product stimulus was presented to each participant, including 3-D images of a product package, as well as flat image views of all four sides of each package with test messaging printed on the packaging as expected in final market placement.

A baseline assessment of risk perception and future intent to use was conducted on VLN® and the four comparator product categories described above. Risk Perception was determined using the Perceived Risk Instrument-Personal ("PRI-P") tool developed and validated in the Phillip Morris Tobacco Heating System research. (Cano, 2018). The VLN® study utilized the portions of this PRI-P that are designed to address consumer perceptions of the health implications and addictiveness of using nicotine-based products.

Prior to initiating the quantitative research for VLN® cigarettes, cognitive testing of the survey instrument was conducted. This exploratory research phase was conducted to ensure that:

1) participants understood all questions and answer choices;

2) responses were consistent with the intended meaning of the questions and answer choices;

3) no critical components of the research were either overlooked or meaningfully altered;

4) specifically, items on the risk perception scale or the intent to use questions would not be misunderstood by participants; and

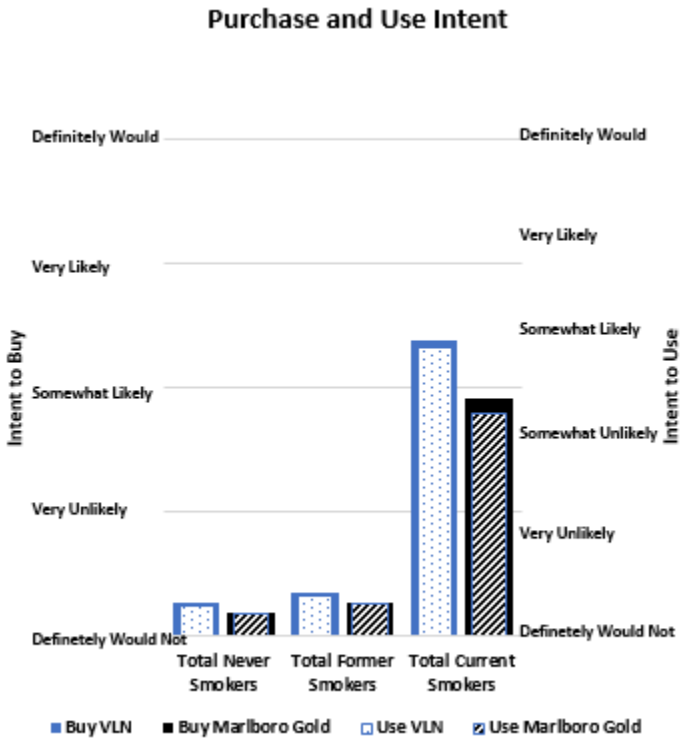
5) neither questions nor answer choices were missing such that the objectives of the study could not be fulfilled.

The cognitive testing identified questions and question structures that, as originally phrased, caused confusion and questionable responses, particularly among never smokers and former smokers, which could only be addressed in the presence of a study moderator. Because the main study was to be conducted online without a moderator in attendance, the cognitive testing served as an important phase for refining the final survey.

3.7.2 *Key findings from VLN® consumer perception studies*

The proposed VLN® products' modified exposure claims did not interest non-smokers, former smokers, or youth (e.g., LA-25): each of these study groups rated the VLN® product concept as being a product that they "definitely would not use."

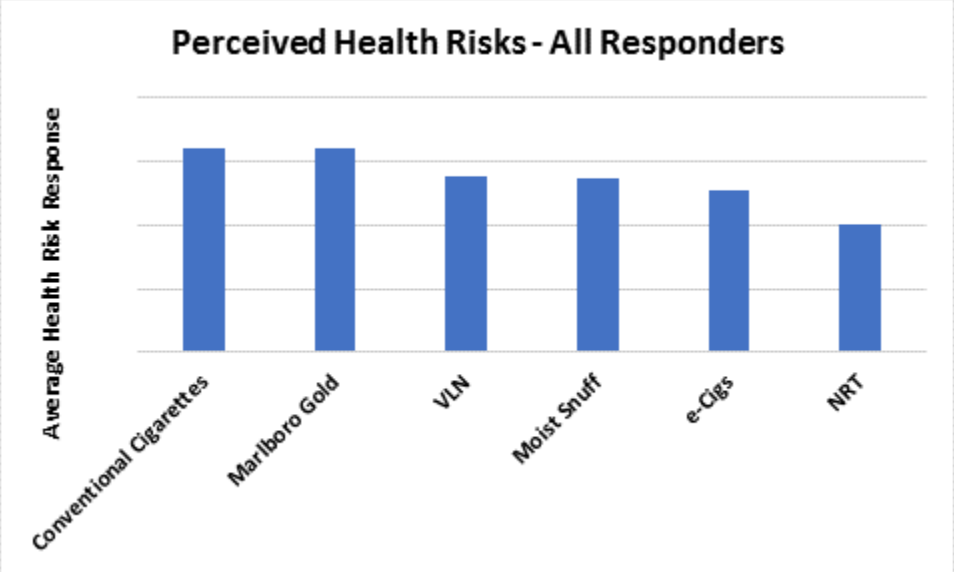
Figure 7: Purchase and Use Intent for VLN® and Marlboro Gold



Only current cigarette smokers expressed any meaningful interest in purchasing or using VLN® cigarettes; the interest and intent observed for VLN® cigarettes were higher than for Marlboro Gold, the number one selling cigarette brand in the U.S

Consumers generally understood the health risks and risk of addiction of tobacco products, as evidenced by their placement of VLN® cigarettes on a continuum of risk next to conventional cigarettes and higher than non-cigarette tobacco products.

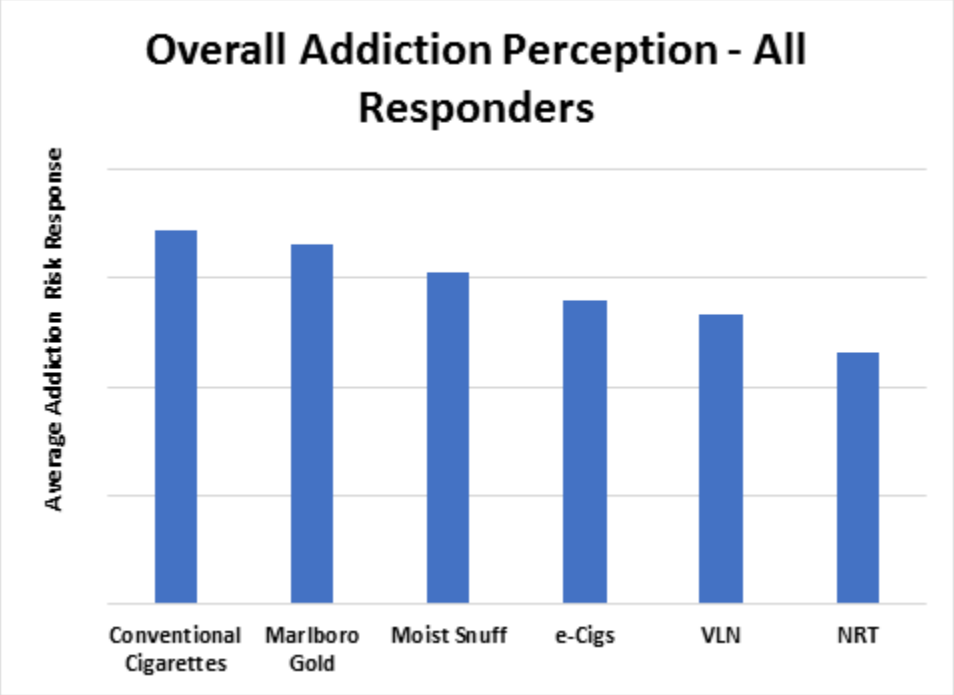
Figure 8: Perceived Health Risk of VLN® and Nicotine Containing Products.



Overall, exposure to the VLN® packaging concept did not change the consumer's perception of the risks of the other tobacco products. In addition, evaluation of the final statements included on the proposed VLN® packs indicated that consumers did not interpret the VLN® packaging or the VLN® exposure modification claims to mean that the VLN® cigarettes were safer than conventional cigarettes. Although some respondents in the qualitative study described VLN® cigarettes as "safer," than conventional cigarettes, the results from the study suggest that such views were attributable to respondents' beliefs regarding the lower likelihood of addiction to VLN® cigarettes and not any perceived intrinsic health benefits regarding the product itself.

Current smokers perceived the risk of addiction of VLN® cigarettes to be between electronic cigarettes and NRT, which suggests that subjects understood that VLN® cigarettes had less nicotine and could be potentially less addicting. Smokers with an intent to quit had a higher perception of the health risks and risk of addiction of tobacco products and VLN® cigarettes than smokers with no intent to quit.

Figure 9: Perceived Addiction Risks of VLN® and Nicotine Containing Product.



The overall results of the study showed that participants understood the modified exposure message and perceived that VLN® cigarettes pose a health risk similar to conventional cigarettes, while the addiction risk was perceived to be between that of e-cigarettes and NRT. Importantly, the results demonstrate that the VLN® modified exposure message did not mislead participants into believing that VLN® is or has been demonstrated to be less harmful or that VLN® poses less health risk as compared to other tobacco products, and thereby satisfies the requirements set forth in §911(g)(2)(B)(iii) of the FD&C Act.

3.8 §911(g)(2)(B)(iv): Issuance of the exposure modification order for VLN® will benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

When it authorized the VLN® PMTAs, FDA determined that XXII's marketing of its VLNC cigarettes would be appropriate for the protection of the public health. (TPL Report, page 10). To make this finding, §910(c)(4) of the FD&C Act required the Agency to consider the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and to take into account (i) the increased or decreased likelihood that existing users of tobacco products

will stop using such products, and (ii) the increased or decreased likelihood that those who do not use tobacco products will start using such products. The standard set forth in §910(c)(4) of the FD&C Act is consistent with standard described in §911(g)(2)(B)(iv). Accordingly, XXII believes that FDA has already made the key determinations with respect to §911(g)(2)(B)(iv) when it authorized the VLN® PMTAs.

Specifically, with respect to current smokers, the TPL Report noted that the available clinical data indicated "that the associated noncancer hazards and cancer risks [of VLN® cigarettes] could be lower compared to marketed cigarettes, as users of products very similar . . . cigarettes tend to decrease their cigarettes per day . . . and puffing volumes if they switch from [normal nicotine content] cigarettes to VLNC cigarettes." (TPL Report, page 7). In addition, results from the qualitative perception tests conducted for XXII show that when exposed to the claims that are the subject of the VLN® MRTPAs, only current cigarette smokers expressed any meaningful interest in trying the product, suggesting that approval of the VLN® MRTPAs could lead to positive benefits for current users of combusted tobacco products.

With respect to persons who do not currently use tobacco products, FDA found that "the limited available evidence on VLNC cigarettes suggests that youth who experiment with VLNC cigarettes may find them less appealing and may be less likely to develop nicotine dependence and become established cigarette smokers due to their lower abuse liability profile." (TPL Report, page 8). Moreover, in announcing its authorization of the VLN® PMTAs, FDA publicly stated that "[t]he agency determined that non-smokers, including youth, are also unlikely to start using the products, and those who experiment are less likely to become addicted than people who experiment with conventional cigarettes." (FDA, December 17, 2019). Results from XXII's consumer perception testing similarly showed that never smokers showed little to no interest in using the product after viewing the proposed modified exposure claims for VLN® cigarettes. Specifically, among all never smokers who evaluated the claim "Helps reduce your nicotine consumption," 95% indicated that they were "somewhat unlikely to use," "very unlikely to use" or "definitely would not use" VLN® on a regular, ongoing basis.

4 CONCLUSION

The nicotine level in XXII's proprietary VLNC cigarettes is at least 95% less as compared to the top 100 cigarette brands in the U.S. marketplace. XXII has developed its proprietary VLNC tobacco and its VLN® cigarettes, for the express purpose of helping adult cigarette smokers to reduce their exposure to nicotine. More than 50 independent clinical studies have been conducted by leading researchers and institutions in the U.S. evaluating XXII's VLNC cigarettes; these studies conclusively demonstrate that use of VLNC cigarettes results in reduced exposure to nicotine, and may result in decreased cigarette consumption, reduction in nicotine absorption, reduction in other biomarkers of exposure, increased quit attempts, a greater number of cigarette-free days and abstinence. VLN® cigarettes and the associated reduced exposure claims have been developed for current, adult smokers with an interest in reducing their nicotine consumption. The challenge in developing modified exposure claims is creating a label, labeling, and advertisements that maximize adult smokers' interest in the product as a substitute for conventional cigarettes, while promoting the idea that such smokers would be better off quitting smoking entirely and minimizing the interest among adult never smokers and former smokers. XXII believes that the proposed reduced exposure claims in the MRTPAs have been scientifically developed and that the evidence submitted in the VLN® MRTPAs fully supports the findings that FDA must make regarding the VLN® MRTPAs in order for the Agency to issue Exposure Modification Orders under §911(g)(2) of the FD&C Act.

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Appendix I

Nicotine Content of VLN® Products Compared to the top 100 US Cigarette Brands sold in the USA.