

# EVALUATING VLN™ CIGARETTES AS MRTPS: CONSIDERATIONS OF MORBIDITY, MORTALITY, AND POPULATION HEALTH

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Section  
911  
FD&C Act

Statutory requirements related to morbidity, mortality, and population health impact



Effect of the proposed modified risk products on morbidity and mortality



Effect of the proposed modified risk products on population health



Likelihood of nonsmokers using VLN™ cigarettes



Likelihood of smokers using VLN™ cigarettes

# SELECT FD&C REQUIREMENTS FOR MORBIDITY, MORTALITY, AND POPULATION HEALTH



(g)(2)  
(A)(iv)

MORBIDITY &  
MORTALITY

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.

(g)(2)  
(B)(iv)

EFFECT ON  
POPULATION

Issuance of an order with respect to the application 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.

# DISCUSSION QUESTIONS 1-3



1

MORBIDITY &  
MORTALITY

Discuss the likelihood that reductions in dependence translate into substantial reductions in morbidities and mortality among individual tobacco users.

2

EFFECT ON  
NONSMOKERS

Discuss the extent to which the following groups are likely to try and progress to regularly using the proposed modified risk tobacco products:

- Never smokers.
- Former smokers.

3

EFFECT ON  
SMOKERS

Discuss the extent to which the following groups will dual use the proposed modified risk products with their usual brand of cigarettes or exclusively use the proposed modified risk products:

- Cigarette smokers who want to quit smoking.
- Cigarette smokers who do not want to quit smoking.

## The applicant's studies:

- Abuse liability studies
- 6-week actual use study
- Consumer perception study

## Peer-reviewed studies:

- Clinical studies of very low nicotine content (VLNC) cigarettes
  - They primarily used SPECTRUM or Quest VLNC research cigarettes
- Epidemiological studies of the effects of reducing cigarettes per day (CPD)



# DISCUSSION QUESTION 1



1

Discuss the likelihood that reductions in dependence translate into substantial reductions in morbidities and mortality among individual tobacco users.

MORBIDITY &  
MORTALITY

# REDUCED ABUSE LIABILITY



The abuse liability of VLN™ cigarettes is significantly reduced compared to normal nicotine content cigarettes, and similar to nicotine replacement therapy (NRT) gum.



After smoking VLN™ cigarettes, blood plasma nicotine levels are 97% lower compared to smoking usual brand, normal nicotine content cigarettes.<sup>1</sup>



Participants rate VLN™<sup>1</sup> and VLNC<sup>2</sup> cigarettes as having lower positive subjective effect ratings (e.g., liking) compared to normal nicotine content cigarettes.



Clinical studies that evaluated CPD after 6 weeks of smoking VLNC cigarettes report reductions ranging from 11% to 46%.<sup>3</sup>

- This range included populations such as people with mental health or substance use comorbidities.



1. The applicant's abuse liability studies.  
2. E.g., Hatsukami et al., 2013; Higgins et al., 2017; Perkin et al., 2018  
3. Donny et al., 2015; Foulds et al., 2018; Hatsukami et al., 2010; Hatsukami et al., 2013; Pacek et al., 2016; Tidey et al., 2017

# CIGARETTES PER DAY (CPD)



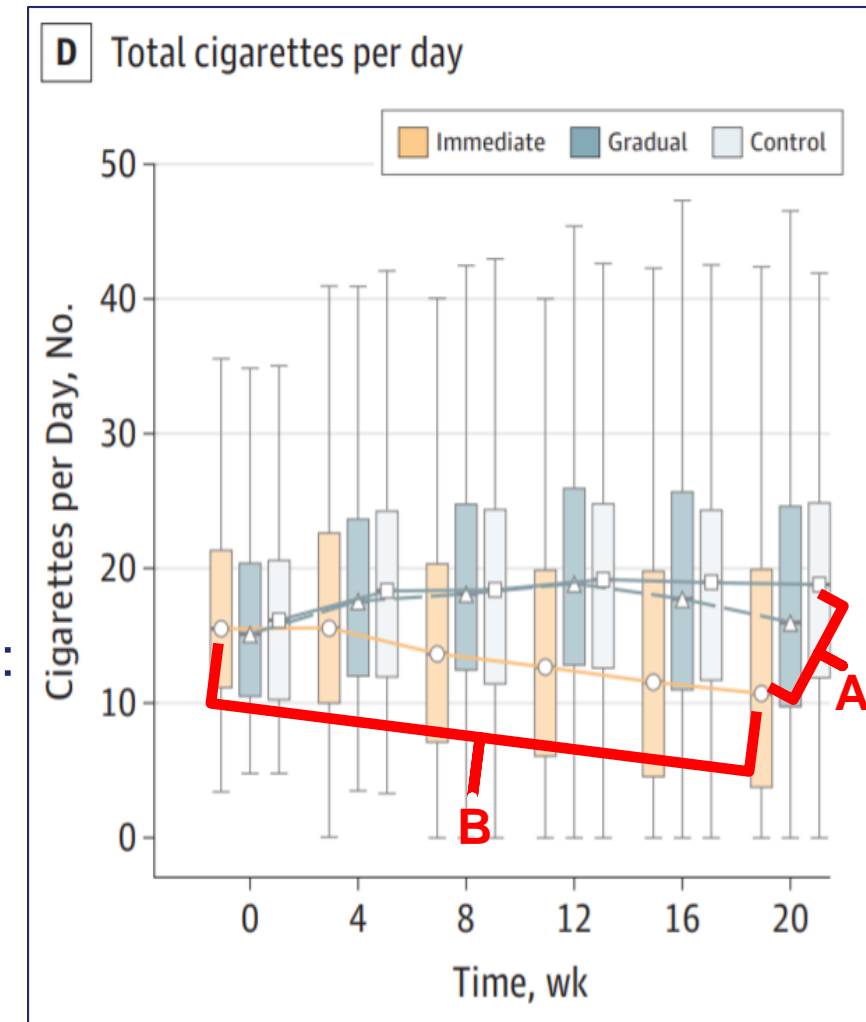
In one study<sup>1</sup> that examined CPD changes over 20 weeks:

- A. CPD was about 50% lower in the VLNC condition compared to the control condition.
- B. Within the VLNC condition, CPD decreased by about a quarter.

 +  CPD decreases even among smokers who dual use VLNC cigarettes with their usual brand, normal nicotine content cigarettes.

Context to consider in these clinical studies<sup>1,2,3</sup> evaluating CPD:

- In most studies, participants were not interested in quitting.<sup>2</sup>
- Participants were instructed to switch to VLNC cigarettes.
- All study cigarettes were provided at no cost.



1. Hatsukami et al., 2018  
2. E.g., Donny et al., 2015; Foulds et al., 2018; Pacek et al., 2016; Tidey et al., 2017  
3. E.g., Hatsukami et al., 2010; Hatsukami et al., 2013



# REDUCED DEPENDENCE



↓ Switching to VLNC cigarettes for 6-20 weeks is associated with decreased dependence scores among smokers interested<sup>1</sup> and not interested<sup>2</sup> in quitting.

🚬 In clinical studies, using VLNC cigarettes may promote quitting.

- Among smokers not interested in quitting, using VLNC cigarettes did not affect motivation to quit, however it did increase quit attempts.<sup>3</sup>
- Among smokers interested in quitting, using VLNC cigarettes along with NRT and behavioral therapy facilitated smoking abstinence.<sup>4</sup>

1. Donny et al., 2015; Walker et al., 2015; Hatsukami et al., 2018

2. Hatsukami et al., 2010

3. Walker et al., 2015; Donny et al., 2015

4. Dermody et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2013; Walker et al., 2012

Compared to smokers who do not reduce their CPD, smokers who reduce their CPD by at least 50% decrease some, but not all, disease risks. For example:



One study found an associated 27% reduction in lung cancer risk.<sup>1</sup>



Some studies found an associated decrease in some cardiovascular risk factors,<sup>2</sup> while another study found no change in risk of myocardial infarction.<sup>3</sup>



Similarly, some studies found an associated decrease in pulmonary symptoms,<sup>4</sup> while others studies found no robust improvements in lung function.<sup>5</sup>

1. Godtfredsen et al., 2005
2. Bolliger, 2000; Bolliger et al., 2002; Eliasson et al., 2001; Hatsukami et al., 2005; Haustein et al., 2004
3. Godtfredsen, 2003
4. Hatsukami et al., 2005; Stein et al., 2005
5. Burchfiel et al., 1995



It is unclear what proportion of smokers who use VLNC cigarettes will reduce their CPD by at least 50%. Thus, the magnitude of the reduction in other morbidities remains unclear.

- In clinical studies,<sup>1</sup> at 6 weeks, smokers assigned to VLNC conditions had cigarette consumption that was 11% to 46% lower compared to baseline.
- In one clinical study<sup>2</sup> comparing CPD at 20 weeks:
  - CPD in the VLNC condition were about 50% that of the control condition.
  - CPD decreased by about a quarter in the VLNC condition, compared to baseline.

1. Donny et al., 2015; Fouldset al., 2018; Hatsukami et al., 2010; Hatsukami et al., 2013; Paceket al., 2016; Tidey et al., 2017

2. Hatsukami et al., 2018

- Studies of different populations have not consistently demonstrated that a reduction in CPD reduces all-cause mortality.<sup>1,2</sup>
  - For example, while one study<sup>1</sup> found a reduction in CPD is associated with a reduction in all-cause mortality, two other studies did not.<sup>2</sup>
  
- The increase in quit attempts and potential increase in quit success associated with using VLNC cigarettes could lead to a decrease in morbidity and mortality.

1. Inoue-Choi, 2019;  
2. Godtfredsen et al., 2002; Tverdal & Bjartveit, 2006



# DISCUSSION QUESTIONS 2 & 3



2

EFFECT ON  
NONSMOKERS

Discuss the extent to which the following groups are likely to try and progress to regularly using the proposed modified risk tobacco products:

- Never smokers.
- Former smokers.

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EFFECT ON  
SMOKERS

Discuss the extent to which the following groups will dual use the proposed modified risk products with their usual brand of cigarettes or exclusively use the proposed modified risk products:

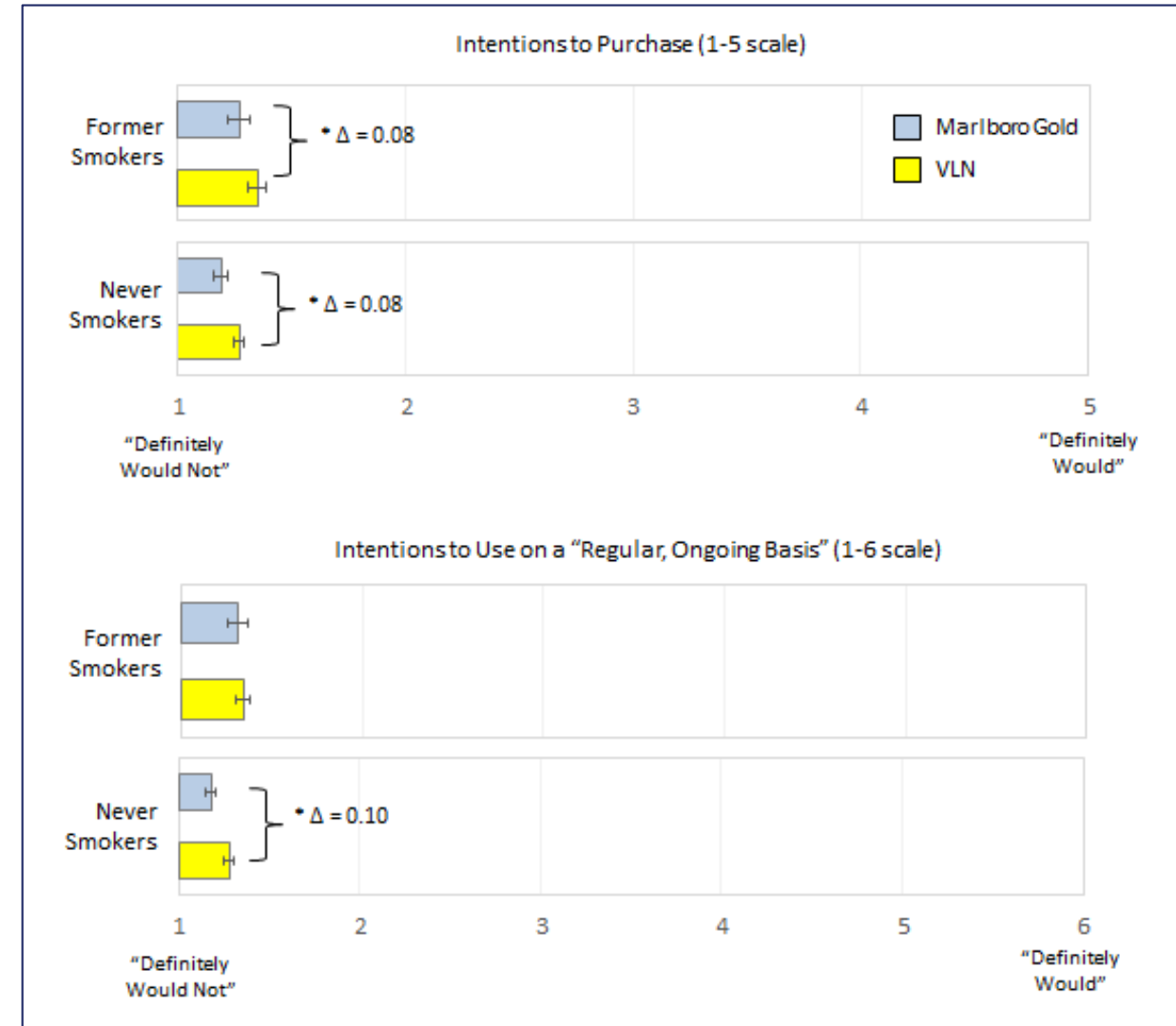
- Cigarette smokers who want to quit smoking.
- Cigarette smokers who do not want to quit smoking.

# THE PROPOSED MRTPS AND NONSMOKER LIKELIHOOD OF USE



In the applicant's consumer perception study, participants were randomized to see VLN™ cigarette packs or Marlboro Gold cigarette packs.

- Nonsmokers reported overall low intentions to purchase and use VLN™ cigarettes.
- Compared to Marlboro Gold cigarettes, nonsmokers reported higher intentions to *purchase* VLN™ cigarettes.
- Compared to Marlboro Gold cigarettes, never smokers (but not former smokers) also had higher intentions to *use* VLN™ cigarettes “on a regular, ongoing basis.”
- Findings were similar for never smokers who were between legal age and 25 years old.



# YOUTH INITIATION AND PROGRESSION TO REGULAR USE



There is no direct evidence to determine whether the products with the proposed claims would affect youth nonusers in the same way as young adult nonusers.

- One study found that other modified risk claims similarly decrease risk perceptions among youth and adults, but affected susceptibility to product use only among adults.<sup>1</sup>
- Exposing youth tobacco nonusers to the products with the proposed claims could increase their risk of initiation.
- The lower abuse liability of VLN™ cigarettes reduces the potential for youth to become regular smokers due to nicotine dependence.

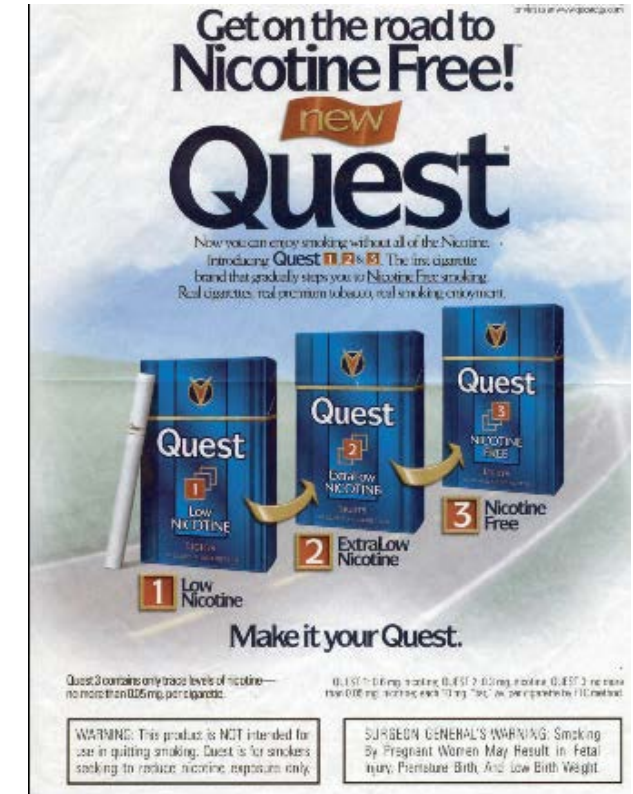
1. El-Touhky et al., 2018

# YOUTH INITIATION AND PROGRESSION TO REGULAR USE



Youth and young adults were not particularly interested in a cigarette brand marketed with similar claims from 2002 to 2010.

- When Quest cigarettes were on the U.S. market and advertised as “low nicotine,” “extra low nicotine,” and “nicotine free,” youth smoking rates declined,<sup>1</sup> indicating a lack of substantial youth uptake of the products.
- College students rated Quest cigarettes as having lower positive expectancies than Marlboro Lights.<sup>2</sup>
- The generalizability of this information is limited, because the applicant proposes to market VLN™ cigarettes using different labeling and advertising.



1. Johnston et al., 2019  
2. O'Connor et al., 2007

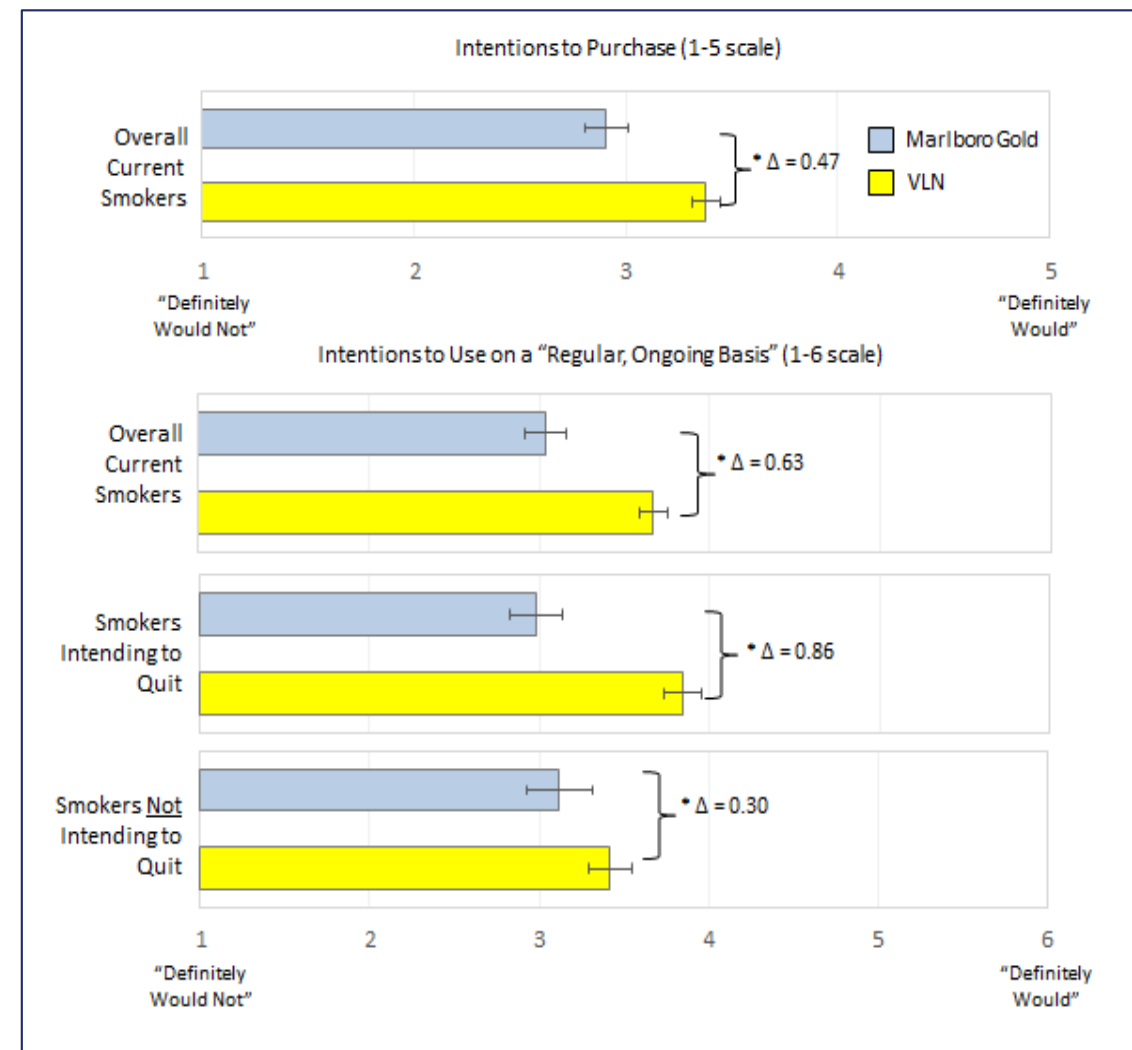


# THE PROPOSED MRTPS AND SMOKER LIKELIHOOD OF USE



In the applicant's consumer perception study, participants were randomized to see VLN™ cigarette packs or Marlboro Gold cigarette packs.

- Overall, smokers reported moderate to high intentions to purchase and use VLN™ cigarettes.
- Compared to Marlboro Gold cigarettes, smokers' intentions to use VLN™ cigarettes were higher.
- Compared to smokers not intending to quit, smokers intending to quit had similar intentions to use Marlboro Gold cigarettes, but higher intentions to use VLN™ cigarettes.





Clinical studies have found that:

- Most smokers who use VLNC cigarettes will decrease their CPD and may increase quit attempts.<sup>1</sup>
- Most smokers do not switch completely to VLNC cigarettes. However, those who primarily use them but continue dual using normal nicotine content cigarettes still experience a decrease in CPD.<sup>1</sup>
- Among smokers interested in quitting, switching to VLNC cigarettes may facilitate smoking abstinence, particularly when used in combination with NRT and behavioral intervention.<sup>2</sup>

1. Donny et al., 2015; Foulds et al., 2018; Hatsukami et al., 2010; Hatsukami et al., 2013; Hatsukami et al., 2018; Pacek et al., 2016; Tidey et al., 2017

2. Dermody et al., 2015; Hatsukami et al., 2010; Hatsukami et al., 2013; Walker et al., 2012

# VULNERABLE SMOKER POPULATIONS



There is little to no evidence that VLNC cigarettes increase risk of adverse effects among smokers with mental illness or substance use disorders.



In smokers with mental health symptoms, using VLNC cigarettes was not associated with increased markers of compensatory smoking compared to the general population.<sup>1</sup>



Although infrequent, there have been reports of adverse events related to nicotine withdrawal in a general population sample among individuals with a history of poor mental health.

E.g., in one study, two subjects were discontinued due to suicidal ideation, assessed as possibly related to VLNC cigarettes and nicotine withdrawal.<sup>2</sup>



Studies also found no evidence that alcohol or marijuana use moderates the effects of VLNC cigarettes.<sup>3</sup>

1. Higginset al., 2017; Tidey et al., 2016  
2. Hatsukami et al., 2018  
3. Pacek et al., 2016; Dermody et al., 2016

# SUMMARY



## 1

### MORBIDITY & MORTALITY

- Marketing VLN™ cigarettes can reduce nicotine dependence among individual tobacco users.
- Because it's unclear what proportion of smokers will reduce their CPD by at least 50%, the magnitude of the reduction in other morbidities and mortality remains unclear.

## 2

### EFFECT ON NONSMOKERS

- Nonsmokers have low intentions to use the VLN™ cigarettes.
- Intentions to purchase VLN™ cigarettes were higher than intentions to purchase Marlboro Gold.
- There is no direct evidence related to youth initiation; we did not identify concerns based on indirect evidence evaluated.

## 3

### EFFECT ON SMOKERS

- Smokers have moderate to high intentions to use VLN™ cigarettes.
- Intentions to purchase and use VLN™ cigarettes were higher than those for Marlboro Gold.
- Studies did not identify significant concerns related to VLNC cigarette use among people with mental illness or substance use disorders.

# DISCUSSION QUESTIONS 1-3



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THE END

