Section VII. Summary of All Research Findings

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VII. Summary of All Research Findings

A. Health Risks of the Tobacco Product.

1. Summary

In many ways VLN™ is just like any other conventional cigarette. Many of its HPHCs are the same level as the leading brands. **22nd Century is making no reduced risk claims about VLN™**. Some smoke constituents, especially nicotine, are reduced in VLN™. These reduced constituents lead to an overall predicted reduced cancer and non-cancer risk. Biomarker of exposure analyses show that the constituents that are reduced in the smoke are actually reduced upon exposure to the smoke. It is clear that use of **VLN™ does not appear to increase health risks**.

The perception of the risks of the product are discussed in the review of the perception study (see Section VIII. Scientific Studies and Analyses. E. Effects of Marketing on Consumer Understanding and Perceptions).

2. The Effect of Marketing VLN™ with Modified Exposure Message on Consumer Perception of the Product

The results of the perception study suggest that participants understood the modified risk message and perceived that VLN™ poses some health and addiction risks. Furthermore, the results demonstrate that the VLN™ modified risk message did not mislead participants into believing that VLN™ is less harmful or that VLN™ poses less health risk as compared to other

tobacco products. Study Subjects placed VLN™ on the continuum of risk in the same area as conventional cigarettes. Compared to Former Smokers and Never Smokers, Current Smokers tended to underestimate the risk of addiction and health effects of all tobacco products including VLN™. Young Never Smokers (legal smoking age to 25-years old) also underestimated the health risks and risks of addiction of all tobacco products including VLN™.

3. The Effect of Marketing VLN™ with Modified Exposure Message on Initiation among Never Smokers

There was very little purchase or use intent by Never Smokers. Compared to Current Smokers, Never Smokers had a higher perception of the health risks and risk of addiction of tobacco products including VLN™. Never Smokers adequately understood the health risks and risk of addiction of VLN™ and demonstrated no interest in the VLN™.

4. The Effect of Marketing VLN™ with a Modified Exposure Message on Youth

There was very little purchase or use intent by subjects legal age to smoke to the age of 25 years old (LA-25). Compared to general population of Never Smokers, LA-25 had a lower perception of the health risks and risk of addiction of tobacco products including VLN™. Youth (LA-25) adequately understood the health risks and risk of addiction of VLN™ and demonstrated no interest in the VLN™.

5. The Effect of Marketing VLN™ with Modified Exposure Message on Initiation among Former Smokers

There was very little purchase or use intent by Former Smokers. Compared to Current smokers, Former Smokers had a higher perception of the health risks and risk of addiction of tobacco products and VLN™. Former Smokers who were long term quitters (> 1 year) tended to rate the tobacco products health and addiction risks slightly higher than recent quitters. Former

Smokers adequately understood the health risks and risk of addiction of VLN™ and demonstrated no interest in the VLN™.

6. The Effect of Marketing VLN™ with Modified Exposure Message among Current Smokers

Current Smokers expressed an intent to purchase and could see themselves using VLN™ cigarettes. The interest and intent were higher than Marlboro Gold, the Number 1 selling cigarette in the United States. Current smokers demonstrated that they understood the health risk of VLN™ by placing VLN™ on the continuum of risk next to conventional cigarettes. Current smokers perceived the risk of addiction of VLN to be between e-cigarettes and NRT, that is, they understood that VLN™ 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™ than Smokers with no intent to quit. Intent to use all nicotine products was asked before and after presentation of the VLN™ product concept. After presenting the VLN™ product concept, the intent to use conventional cigarettes, e-cigarettes and NRT decreased. This suggests that participants of this study showed an interest in shifting away from nicotine products to products having lower levels of nicotine.

7. HPHC's and Quantitative Risk Assessments

The chemistry of the smoke from VLN™ has been measured under ISO and Canadian Intense (CI) smoking conditions[1]. When compared to the top king size market leading brands, VLN™ yields lower nicotine and a number of other toxic constituents (Table VII.A-1)[2]. Smoke constituents that are markedly different include (greater than 2x):

- Benzo[a]pyrene
- Formaldehyde
- Nicotine

[1] See Section VIII.B.2.i HPHC Analysis on VLN™ under ISO and Canadian Intense Conditions
[2] See Section VIII.B.2.iii HPHC Analysis on Market Leading Brands.

- NNK
- NAT
- NAB

A quantitative risk analysis was performed on VLN™ regular and menthol comparing them to the leading brands[3]. This analysis shows that VLN™ does not present an increased cancer or non-cancer risk when compared to leading brands. Table VII.A-2., *Summary of Product Cancer Risks*, lists the respective cancer risks under ISO conditions. Figure VII.A-1 shows the cancer risks. The upper and lower 95% confidence limits of the risk are presented. The range of risk from VLN™ is less than and different from the market leading brands. Table VII.A-3., *Summary of Product Non-Cancer Risks,* lists the non-cancer risks of each product under ISO smoking conditions and Figure VII.A-2 shows the non-cancer risks. The range of risk from VLN™ is less than and different from the market leading brands. A sub-analysis indicated that the risks of respiratory disease less than and different from the leading brands[4]. Reproductive risks were not different. Because of the limited constituents contributing to cardiovascular risks, an analysis could not be performed.

Table VII.A-1.Summary of HPHC Results of VLN™ and Market Leading Brands

ISO Smoking Conditions		VLN™ King	VLN™ Menthol King	Camel Blue King	Marlboro Gold King	Marlboro Menthol Gold King	Marlboro Red King	Marlboro Special Blend Gold King	Newport Menthol Green King
Constituent	**Unit**								
Acetaldehyde	(µg/cig)	647 (56)	678 (62)	597 (51.2)	649 (35.5)	547 (33.4)	783 (40.3)	595 (29.0)	1005 (29.1)
Acrolein	(µg/cig)	29.6 (3.3)	30.1 (2.8)	55.7 (5.13)	59.7 (3.35)	48.9 (3.46)	69.8 (4.56)	54 (3.41)	92 (3.59)
Acrylonitrile	(µg/cig)	11.5 (0.8)	12.0 (0.5)	7.46 (0.716)	6 55 (0.493)	5.23 (0.605)	9.24 (0.800)	5.79 (0.924)	12.1 (0.908)
Aminobiphenyl, 4-	(ng/cig)	1.57 (0.11)	1.55 (0.06)	1.33 (0.08)	1 23 (0 5)	1.19 (0.06)	1.34 (0.05)	1.17 (0.07)	1.55 (0.06)
Aminonaphthalene, 1-	(ng/cig)	10.1	9.71 (0.78)	12.4 (0.3)	12.5	12.3	14.6	12.4	14.3

[3] See section VIII.B.3 Quantitative Risk Assessment.
[4] See section VIII.B.3 Quantitative Risk Assessment.

ISO Smoking Conditions		VLN™ King	VLN™ Menthol King	Camel Blue King	Marlboro Gold King	Marlboro Menthol Gold King	Marlboro Red King	Marlboro Special Blend Gold King	Newport Menthol Green King
		(1)			(0.7)	(0.5)	(0.6)	(0.2)	(0.2)
Aminonaphthalene, 2-	(ng/cig)	5.63 (0.44)	5.54 (0.29)	7.06 (0.25)	7 26 (0.41)	6.89 (0.24)	7.87 (0.23)	7.08 (0.27)	1.17 (0.07)
Ammonia	(µg/cig)	30.1 (5.0)	34.3 (3.4)	12.7 (0.788)	12.3 (0.691)	9.15 (0.684)	17.3 (0.838)	12.0 (0.89)	18.8 (1.27)
Benzene	(µg/cig)	37.8 (2.2)	39.2 (1.7)	31.9 (2.88)	28.6 (2.65)	26.0 (3.0)	35.7 (2.71)	25.6 (2.99)	43.3 (2.86)
Benzo[a]pyrene	(ng/cig)	2.84 (0.15)	2.97 (0.27)	7.07 (0.39)	6 26 (0.29)	6.8 (0.30)	8.70 (0.65)	6.19 (0.51)	9.10 (0.77)
Butadiene, 1,3-	(µg/cig)	34.5 (1.3)	36.3 (1.7)	46.6 (4.27)	46.4 (4.84)	40.3 (2.69)	54.7 (5.02)	41.3 (5.08)	69.9 (6.58)
Carbon Monoxide	(mg/cig)	11.8 (0.6)	12.3 (0.7)	10.9 (0.7)	10.2 (0.6)	9.90 (0.54)	13.3 (0.90)	9.92 (0.64)	15.1 (1.1)
Crotonaldehyde	(µg/cig)	12.6 (1.5)	13.4 (1.3)	13.0 (1.59)	14.7 (1.62)	12 (1.17)	21.9 (1.89)	12.8 (0.891)	26.9 (0.76)
Formaldehyde	(µg/cig)	6.32 (0.45)	5.93 (0.6)	18.6 (2.71)	20.7 (2.76)	24.6 (2.15)	30.7 (4.84)	18.0 (1.79)	40.2 (4.01)
Isoprene	(µg/cig)	332 (15)	347 (12)	393 (35.2)	395 (34.2)	334 (28.8)	468 (21.1)	345 (40.5)	570 (49.1)
Nicotine	(mg/cig)	0.0246 (0.0015)	0.0257 (0.0012)	0.837 (0.028)	0.670 (0.026)	0.741 (0.036)	0.956 (0.055)	0.675 (0.039)	1.08 (0.05)
NNK	(ng/cig)	12.5 (1.2)	11 (0.8)	46.1 (1.29)	67.0 (3.6)	76.2 (3.83)	96.8 (6.97)	66.4 (2.53)	62.1 (4.29)
NNN	(ng/cig)	62 (2.2)	58.2 (1.9)	74.0 (3.60)	86.2 (4.31)	87.7 (8.48)	125 (4.85)	91.4 (6.02)	102 (10.5)
NAB	(ng/cig)	1.39 (0.11)	1.24 (0.13)	12.8 (0.592)	13.2 (0.404)	12.9 (0.556)	17.9 (0.485)	13.8 (0.402)	17.1 (0.929)
NAT	(ng/cig)	5.48 (0.46)	5.0 (0.33)	101 (4.13)	107 (3.66)	104 (4.79)	158 (4.24)	111 (3.39)	145 (8.95)
NO	(µg/cig)	179 (7)	176 (12)	163 (31)	148 (26)	131 (21)	173 (26)	155 (22)	195 (28)
NOx	(µg/cig)	301 (12)	296 (24)	288 (53)	260 (45)	226 (25)	322 (54)	270 (34)	383 (63)
Toluene	(µg/cig)	60.3 (4.5)	64.6 (3.0)	57.2 (4.87)	50.6 (4.03)	44.0 (4.66)	64.9 (4.12)	44.5 (4.71)	82.7 (4.87)
Tar	(mg/cig)	6.98 (0.4)	7.37 (0.39)	9.84 (0.53)	8 97 (0.55)	9.44 (0.55)	14.0 (1.0)	8.87 (0.55)	15.4 (1.0)
Water	(mg/cig)	0.466 (0.146)	0.490 (0.114)	0.997 (0.159)	0.751 (0.145)	0.779 (0.182)	1.96 (0.37)	0.747 (0.131)	3.17 (0.76)
Puffs	(#/cig)	5.76 (0.17)	5.85 (0.17)	8.14 (0.21)	7 29 (0.21)	7.48 (0.25)	7.30 (0.29)	7.43 (0.25)	7.32 (0.31)
Menthol	(mg/cig)	Not Measured	0.432 (0.027)	Not Measured	Not Measured	0.376 (0.0268)	Not Measured	Not Measured	0.481 (0.0194)
Date of testing		5/30/2018	5/30/2018	9/5/18	9/5/18	9/5/18	9/5/18	9/5/18	9/5/18

ISO Smoking Conditions	VLN™ King	VLN™ Menthol King	Camel Blue King	Marlboro Gold King	Marlboro Menthol Gold King	Marlboro Red King	Marlboro Special Blend Gold King	Newport Menthol Green King
Laboratory	Enthalpy Analytical	Enthalpy Analytical	Enthalpy Analytical	Enthalpy Analytical	Enthalpy Analytical	Enthalpy Analytical	Enthalpy Analytical	Enthalpy Analytical
Publication/ Report No.	Project Code: 0318-026 [pg 92]	Project Code: 0318-026 [pg 92]	Project Code: 0718-022 [pg 92]	Project Code: 0718-022 [pg 92]	Project Code: 0718-022 [pg 92]	Project Code: 0718-022 [pg 92]	Project Code: 0718-022 [pg 92]	Project Code: 0718-022 [pg 92]

Table VII.A-2. Summary of Product Cancer Risks.

Product	Cancer Risk	95% LCL	95% UCL	% Change From VLN™
VLN™ King	0.327	0.299	0.356	-
Camel Blue	0.504	0.482	0.547	+35%
Marlboro Gold	0.502	0.484	0.539	+35%
Marlboro Special Blend Gold	0.450	0.426	0.475	+27%
Marlboro Red	0.721	0.676	0.786	+55%
VLN™ Menthol King	0.351	0.325	0.377	-
Marlboro Menthol Gold	0.435	0.405	0.464	+19%
Newport Menthol Green	0.881	0.858	0.904	+60%

Figure VII.A-1.Total Cancer Risk of VLN™ Compared to Market Standards. (Upper and lower 95% confidence intervals of the risk estimates are shown).

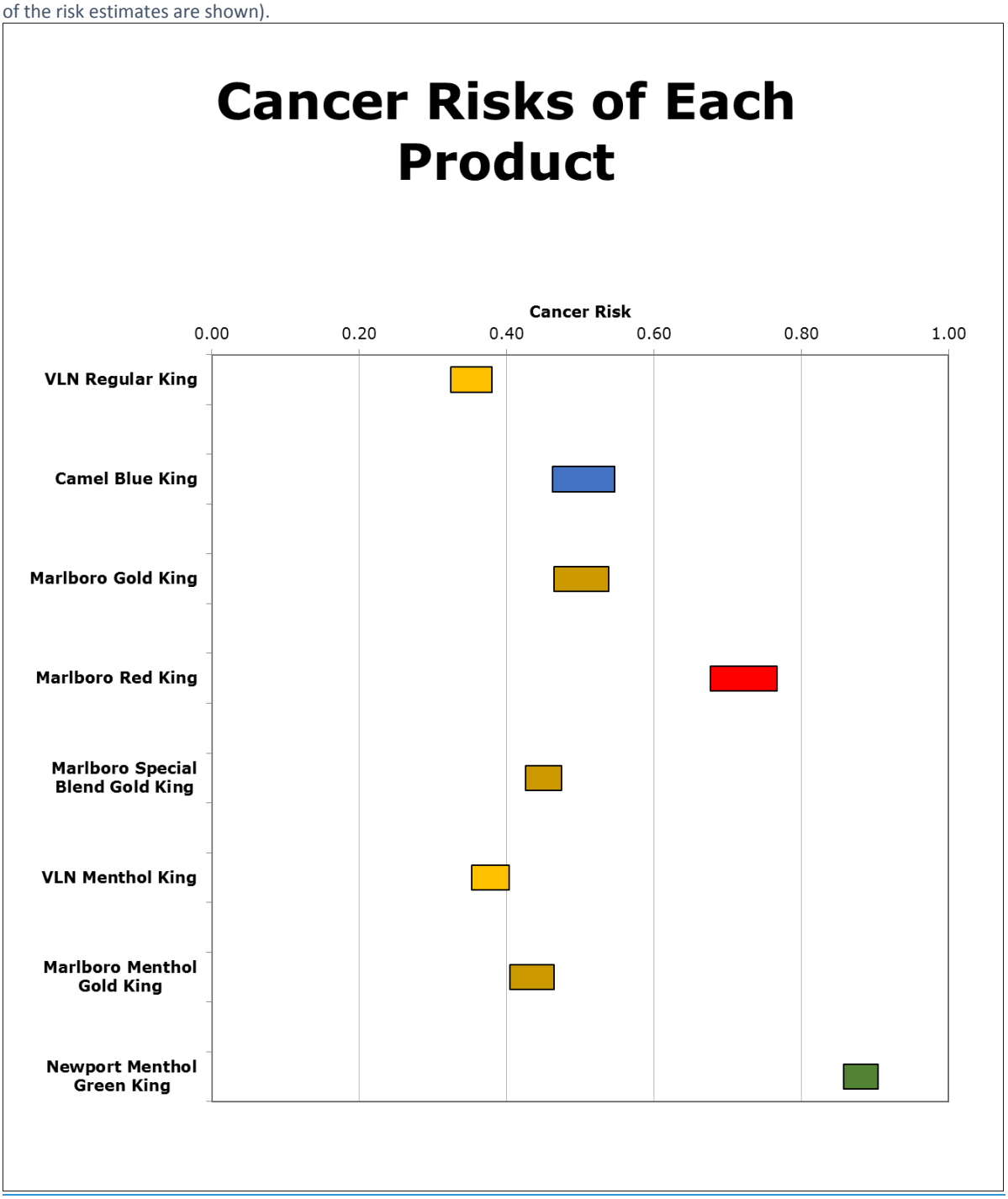
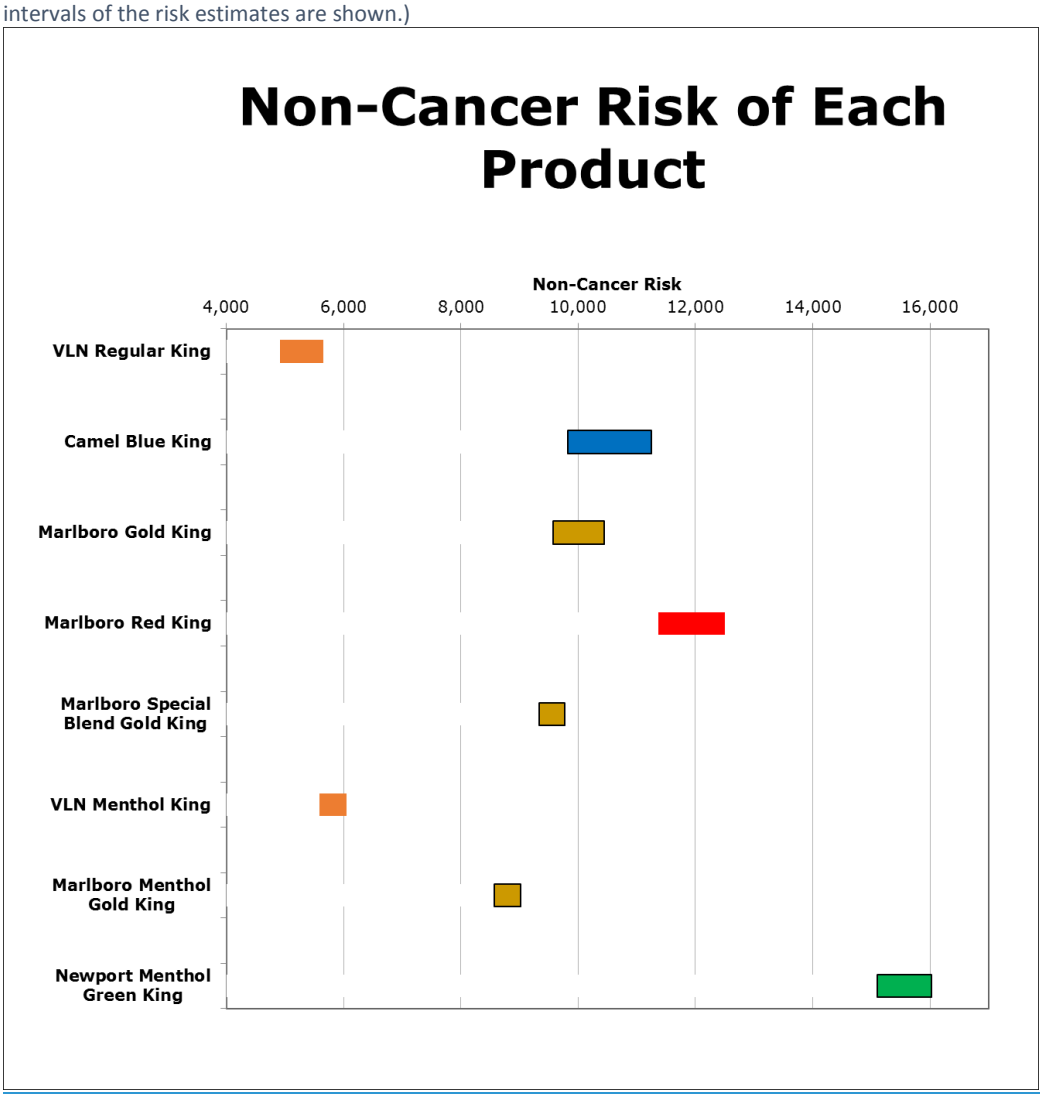


Table VII.A-3. Summary of Product Non-Cancer Risks.

Product	Non-Cancer Risk	95% LCL	95% UCL	% Change From VLN™
VLN™ King	5290	4910	5660	-
Camel Blue	10500	9830	11200	+50%
Marlboro Gold	10000	9570	10400	+47%
Marlboro Special Blend Gold	9340	8900	9780	+43%
Marlboro Red	11900	11400	12500	+56%
VLN™ Menthol King	5590	5180	5890	-
Marlboro Menthol Gold	8570	8130	9020	+35%
Newport Menthol Green	15600	15100	16000	+64%

Figure VII.A-2. Total Non-Cancer Risk of VLN™ compared to market leading brands. (Upper and lower 95% confidence intervals of the risk estimates are shown.)



The goal of the risk assessment process was to predict if changes in HPHC's would likely result in a change in risks. Because of the differences in selected smoke constituents, it is reasonable to expect that relevant biomarkers of exposure would also be reduced[5]. Figure VII.A-3 shows the reduction in total nicotine equivalents (TNE) after 20-week of use of SPECTRUM

[5] See Section VII.G. Claims Support for a review of the reduction in CPD and biomarkers of exposure.

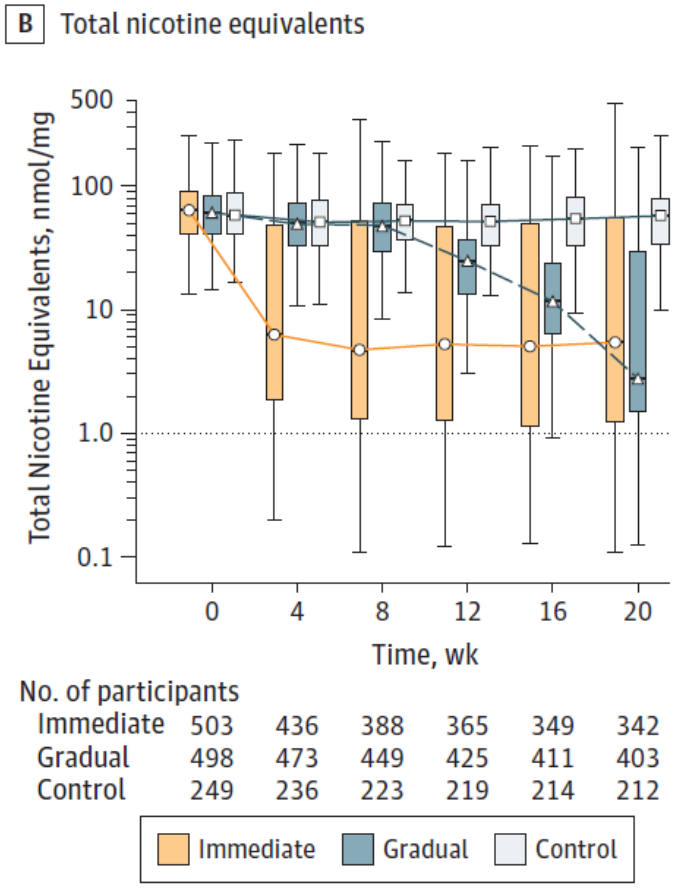
(VLN™) compared to normal nicotine content cigarettes (NNC). TNE was statistically significantly reduced from 51.87 to 21.45 nmol/mg creatinine (Hatsukami *et al*. 2018 [pg. 94]). Acrolein is reduced by almost 50% in VLN™ smoke (Table VII.A-1). 3-HMPA is a metabolite of acrolein. It was statistically significantly reduced after 20-weeks of use of SPECTRUM (VLN™) from 7.67 to 6.05 nmol/mg creatinine (Figure VII.A-4). 3-HMPA was reduced by 47% after 6-weeks of use of Quest 3 (Hatsukami et al 2010 [pg 94]) NNK is reduced from 75 to 90% in the smoke of VLN™ compared to the leading brands (Table VII.A-1). NNAL is the metabolite of NNK. NNAL was statistically significantly reduced after 20 weeks of use of Spectrum (VLN™) from 1.14 to 0.74 pmol/mg creatinine (Figure VII.A-5). NNAL was reduced 32% after 6-weeks of SPECTRUM

(Donny *et al*. 2015 [pg 92]), 57% after 6-weeks of use of Quest 3 (Hatsukami *et al*. 2010 [pg 94]) and 47% after 8-weeks of use of SPRECTUM (Hatsukami *et al*. 2017 [pg 94]). Benzo[a] pyrene is a polycyclic aromatic hydrocarbon and is reduced at least by 50% in VLN™ when compared to leading brands (Table VII.A-1). Urinary phenanthrene tetraol (PheT) is an indicator of exposure to polycyclic hydrocarbons (PAH). PheT was statistically significantly reduced from 2.16 to 2.06 pmol/mg creatinine (Figure VII.A-6). A metabolite of pyrene, 1-HOP, is also an accepted biomarker of PAHs. Use of Quest 3 resulted in a reduction of 1-HOP from 0.73 to 0.57 after 6-weeks of smoking (Hatsukami *et al*. 2010 [pg 94]). It was reduced by 17% after 7 days of smoking Quest 3 (Hammond and O'Connor 2014 [pg 94]). Ding (Ding *et al*. 2014 [pg 92]) did not observe a change in 1-HOP after 7 days of smoking Quest 3. Benzene and acrylonitrile are not reduced in the smoke of VLN™ compared to the market leading brands but the respective biomarkers SPMA

and CEMA are reduced (Table VII.A-1)[6]. SPMA was reduced from 1.35 to 0.76 after 6-weeks of use of Quest 3 (Hatsukami *et al*. 2010 [pg 94]).

These HPHC and biomarker results along with the risk assessment predictions suggest that VLN™ will not result in an increase in exposure to identified toxic materials in smoke. The innate reduced levels of certain toxic constituents in VLN™ smoke as well as the reduced CPD is likely to result in reduced exposures and possibly reduced health risks.

Figure VII.A-3. Total nicotine equivalents (TNE) after 20-weeks (From Hatsukami *et al*. 2018 [pg94]).



[6] This could be due to differences in the smoke of the leading brands compared to the NNC cigarettes. An additional explanation could be that because of the reduction in CPD, there was a measured reduction in the biomarkers.

Figure VII.A-4. 3-HMPA levels after 20 weeks of use (note log scale) (From Hatsukami *et al*. 2018 [pg94])

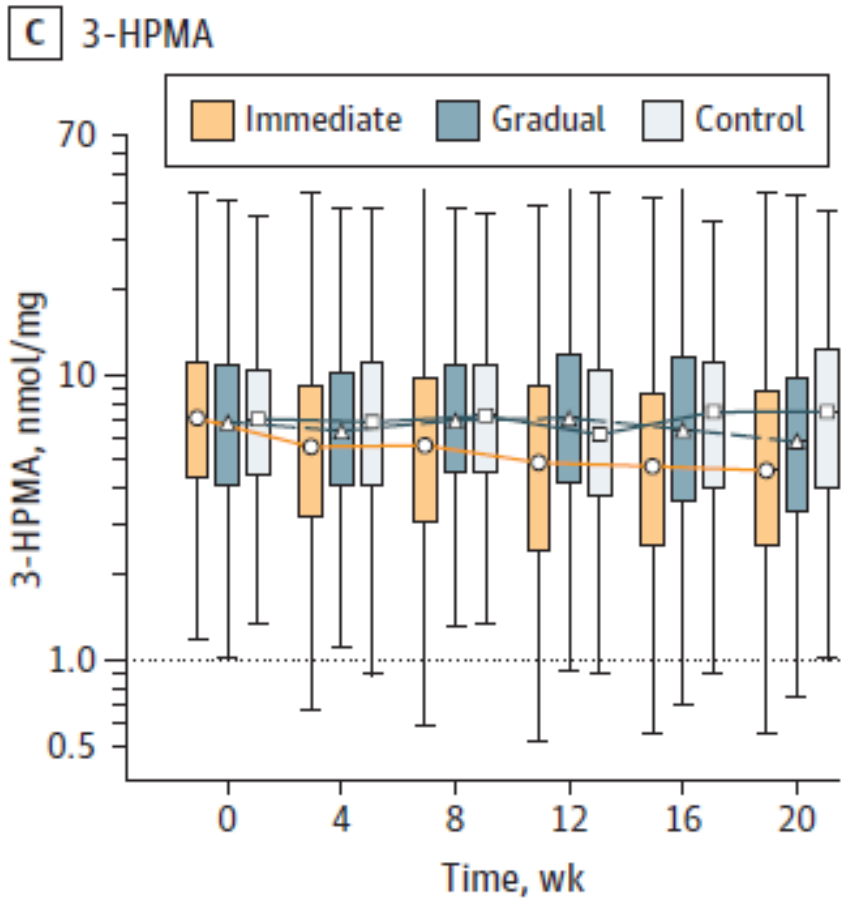


Figure VII.A-5. NNAL levels after 20 weeks of use (note log scale) (From Hatsukami *et al*. 2018 [pg94])

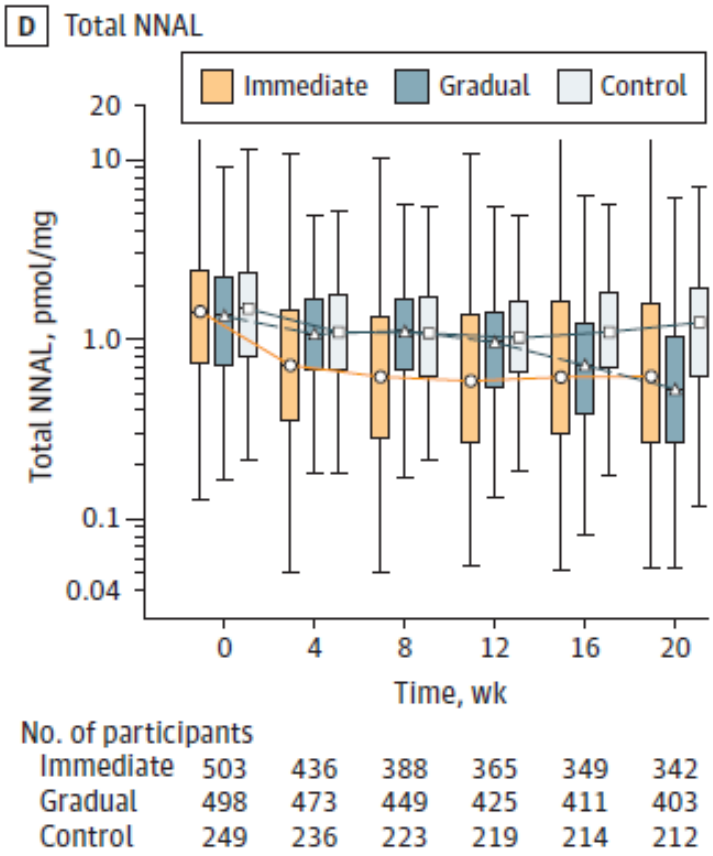


Figure VII.A-6. PheT levels after 20 weeks of use (note log scale) (From Hatsukami *et al*. 2018 [pg 94])

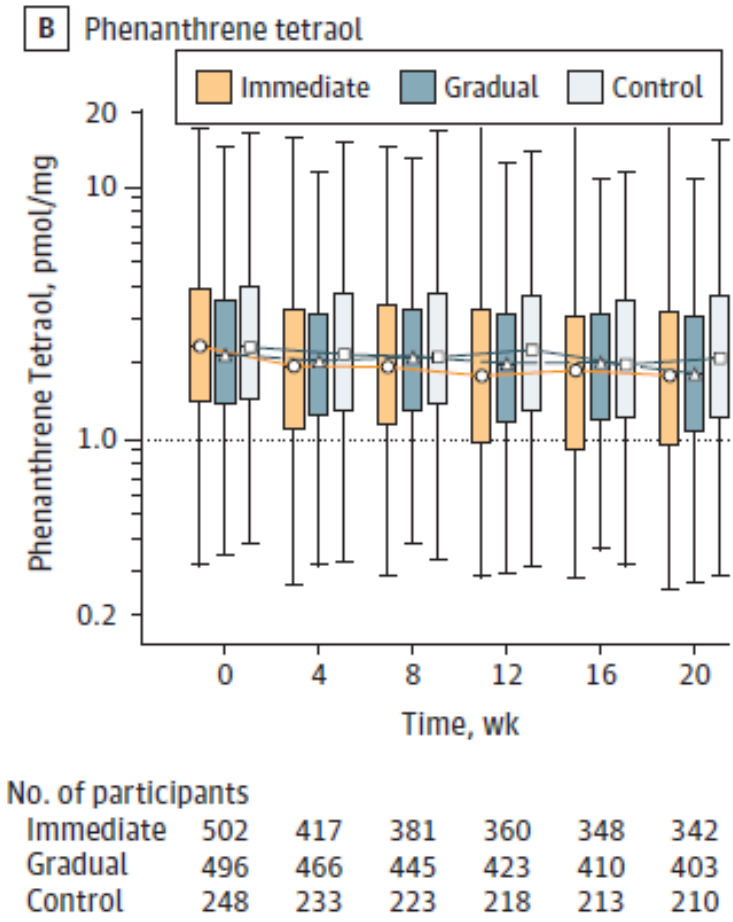
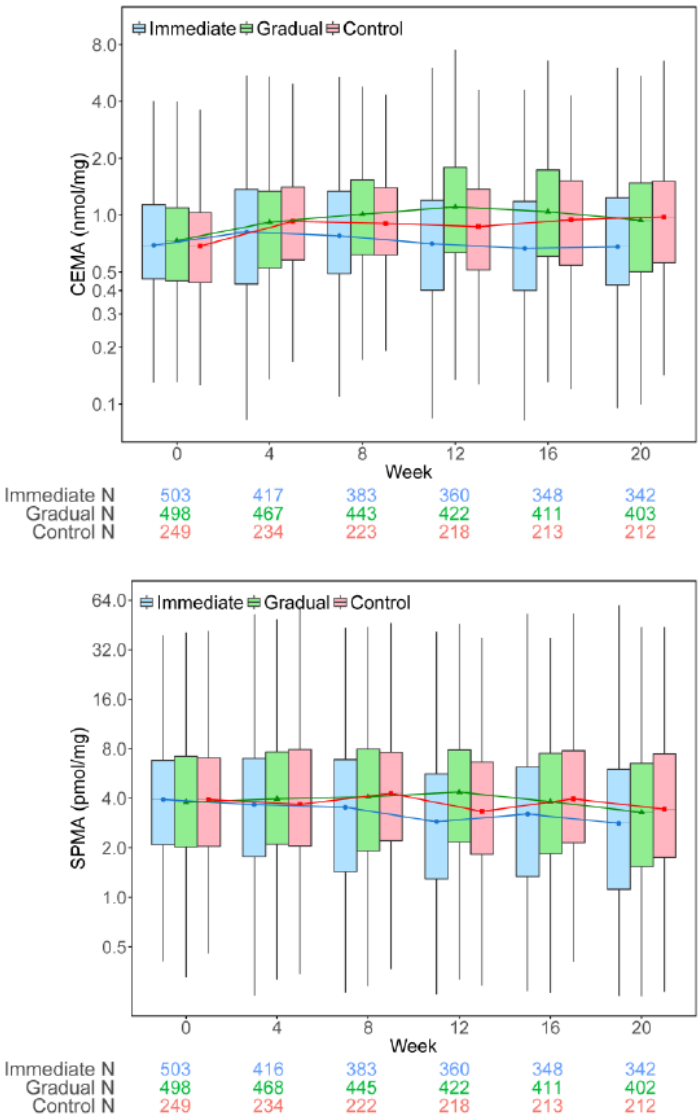


Figure VII.A-7. Additional biomarkers of exposure (From Hatsukami *et al*. 2018 [pg 94]).



8. Unintended Consequences

It is well known that quitting smoking results in weight gain. It appears that use of VLN™ may result in weight gain also.

Cigarette smoke is known to induce clot formation. Nicotine has experimentally been shown to inhibit platelet activation. It has been suggested that VLNC cigarettes could put smokers

at an increased risk. There is no clinical evidence to suggest that use of VLN™ is associated cardiovascular disease.

i. Weight Gain

The relationship between smoking cessation and weight gain is well established. Smokers weigh less than non-smokers and smoking cessation is typically accompanied by weight gain, on average, of 4.5 kg within a year of abstinence (Veldheer *et al*. 2015 [pg 101]; Audrain-McGovern and Benowitz 2011 [pg 89] ; Aubin *et al*. 2012 [pg 89]). Nicotine in cigarettes is likely responsible for the weight-reducing effects of smoking. Use of the transdermal nicotine patch or nicotine gum (Gross *et al*. 1989 [pg 93]) during quit attempts attenuates cessation-induced weight gain, typically in a dose-related manner. Taken together, evidence points to reductions in nicotine exposure as mediating cessation-induced weight gain, and thus, weight gain is a likely outcome of nicotine reduction. (Benowitz *et al*. 2012 [pg 90]). As such, one consequence of a nicotine reduction in VLNC cigarettes may be weight gain.

Benowitz (Benowitz *et al*. 2007 [pg 90]) conducted a 10-week longitudinal study in 20 subjects where the smokers had their cigarette nicotine gradually reduced[7]. Body weight initially increased significantly by an average of 0.9 kg over 6-weeks. The changes lessened and were nonsignificant by 10 weeks (Table VII.A-4). Rupprecht (Rupprecht *et al*. 2017 [pg 99]) looked at the effect of abrupt switching to SPECTRUM cigarettes on current smokers. There was no difference in the weight gain at weeks 1 through 6 when comparing SPECTRUM to NNC or usual brand. However, when the data was parsed to look at only compliant subjects, there was a weight gain

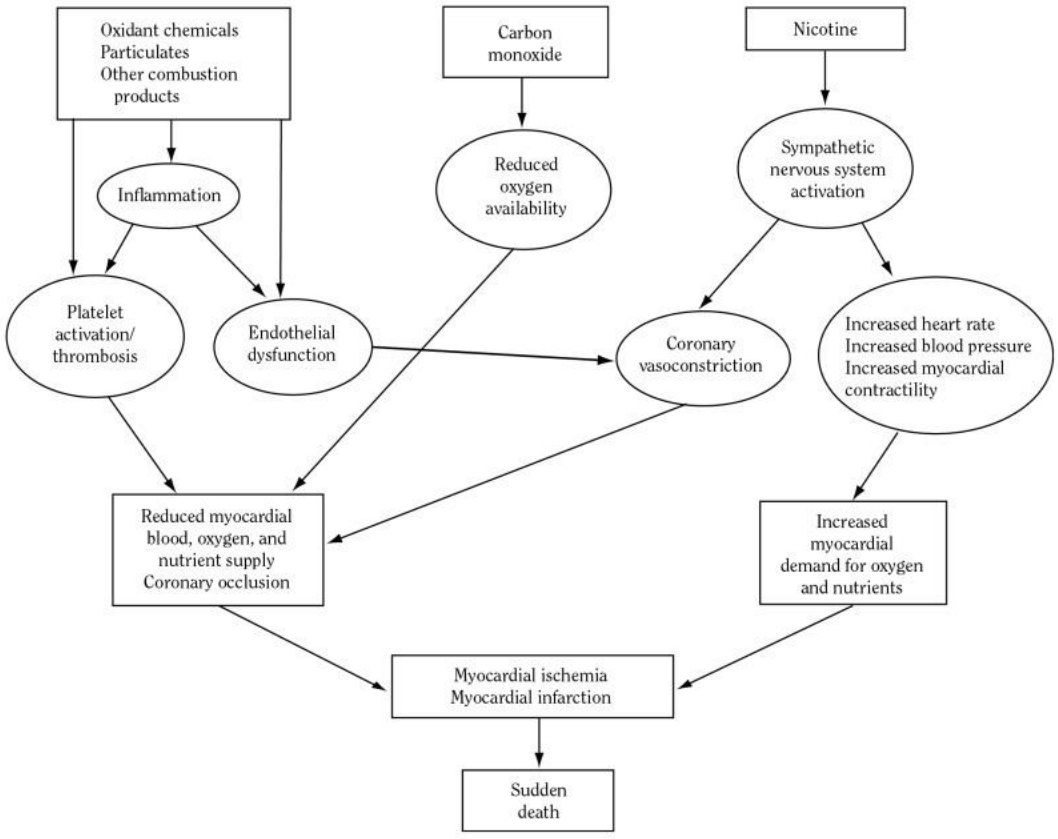
[7] The cigarettes were not SPECTRUM. They were research cigarettes produced by Philip Morris using CO_2 extraction to remove the nicotine.

of about 1.5 kg after 6 weeks. Compliant women gained more weight than compliant men. These results suggest that weight gain is a likely consequence of use of SPECTRUM cigarettes.

ii. Platelet Activation

Cardiovascular disease due to cigarette smoking manifests itself in the form of venous thrombosis, stroke, and myocardial infarction. Benowitz (Benowitz *et al*. 2007 [pg 90]) reviewed the overall role of smoking and developed a model of the disease (Table VII.A-4). Platelet activation is part of the process but is not the only event leading to CVD.

Figure VII.A-8. Model by which cigarette smoking causes an acute cardiovascular event (From Benowitz 2003 [pg 90])



Platelets play a major role in clot formation. Ramachandran *et al*.(2004) [pg 99] found that cigarette smoke increases platelet activation and the activation is inhibited by nicotine *in vitro*. Girdhar *et al*. (2008, *Nicotine & Tobacco Research* [pg 93]) investigated whether nicotine

protects smokers' platelets against smoke induced platelet activation *in vivo*. Subjects smoked either normal nicotine cigarettes or Quest 3 and platelet activation state (PAS) was measured. There was an increased in PAS after use of Quest 3. The authors postulated that VLNC cigarettes may increase harm in conventional cigarette smokers when they transition to VLNC cigarettes because of the lack of the nicotine protective effect. Benowitz (Benowitz *et al*. 2007 [pg 90]) conducted a 10-week longitudinal study in 20 subjects where the smokers had their cigarette nicotine gradually reduced[8]. Data was collected during the first week while smokers used their usual brand. Progressively lower nicotine content cigarettes were smoked over the next 5 weeks ending with a 0.6 mg nicotine cigarette. The subjects were then allowed to return to smoking their normal brand (or quit). Cardiovascular effect biomarkers were evaluated (Table VII.A-4). Cardiovascular biomarkers showed no evidence of a more adverse risk profile when the subjects smoked VLNC cigarettes.

Table VII.A-4. Cardiovascular biomarkers (From Benowitz *et al*. 2007 [pg 90]).

	Week 1, mean (95% CI)	Week 6, mean (95% CI)	Week 10, mean (95% CI)	% difference week 6 versus week 1, mean (95% CI)	% difference week 10 versus week 1, mean (95% CI)	% difference week 10 versus week 6, mean (95% CI)
Body weight (kg)	71.4 (65.8-77.1)	72.3 (66.7-78.0)	72.0 (66.4-77.7)	**1 (0-2)**	1 (0-2)	0 (−1-1)
Systolic blood pressure (mm Hg)	122 (116-129)	124 (116-132)	123 (117-130)	1 (−4-7)	1 (−5-7)	−1 (−8-7)
Diastolic blood pressure (mm Hg)	79.0 (73.4-84.6)	76.6 (71.9-81.2)	78.8 (74.9-82.8)	−3 (−10-4)	0 (−9-8)	3 (−3-9)
Heart rate	76.0 (71.2-80.7)	72.9 (67.2-78.5)	79.8 (73.7-86.0)	−4 (−12-3)	5 (−6-16)	10 (−3-22)
WBC count (1,000)	7.3 (6.5-8.2)	7.7 (6.9-8.4)	7.6 (6.5-8.8)	4 (−6-15)	4 (−11-20)	0 (−15-15)
Hemoglobin (%)	14.7 (14.1-15.2)	14.4 (13.8-14.9)	14.4 (13.9-14.9)	−2 (−4-0)	−2 (−4-0)	0 (−2-2)
HDL cholesterol (ng/dL)	49.9 (40.9-58.8)	51.2 (43.3-59.0)	51.5 (42.3-60.7)	3 (−7-12)	3 (−6-13)	1 (−9-10)
C-reactive protein* (mcg/mL)	1.00 (0.59-1.68)	1.32 (0.72-2.42)	1.25 (0.67-2.35)	33 (−26-136)	26 (−36-148)	−5 (−57-107)
sICAM* (ng/mL)	241 (219-265)	253 (219-293)	229 (207-253)	5 (−6-18)	−5 (−12-2)	−10 (−18-0)
Fibrinogen *,† (mg/dL)	247 (223−273)	263 (232-298)	259 (243-275)	7 (−4-18)	5 (−9-21)	−2 (−16-16)
IL-6* (pg/mL)	1.02 (0.76-1.37)	0.97 (0.71-1.31)	1.16 (0.77-1.74)	−5 (−26-22)	14 (−28-80)	20 (−19-77)
P-selectin* (ng/mL)	40 (35-45)	41 (35-48)	40 (35-46)	3 (−6-13)	1 (−5-7)	−3 (−14-10)

NOTE: Week 1 is while smoking usual brand. Week 6 is while smoking the lowest RNC cigarette (1 mg). Week 10 is 4 weeks after the end of RNC smoking. Values in bold indicate significant differences ($P < 0.05$).
*Geometric means.
†$n = 11$.

[8] The cigarettes were not SPECTRUM. They were research cigarettes produced by Philip Morris using CO_2 extraction to remove the nicotine.

It is not clear if the effect of reduced nicotine in cigarettes will actually manifest itself as a changed in disease risk. Joel *et al*. (2012) [pg 95] reviewed the potential consequences of VLNC cigarettes on cardiovascular disease. It was their belief that overall CVD risk in the U.S. could be dramatically reduced by reduction of nicotine in cigarettes. This conclusion was based on the following points:

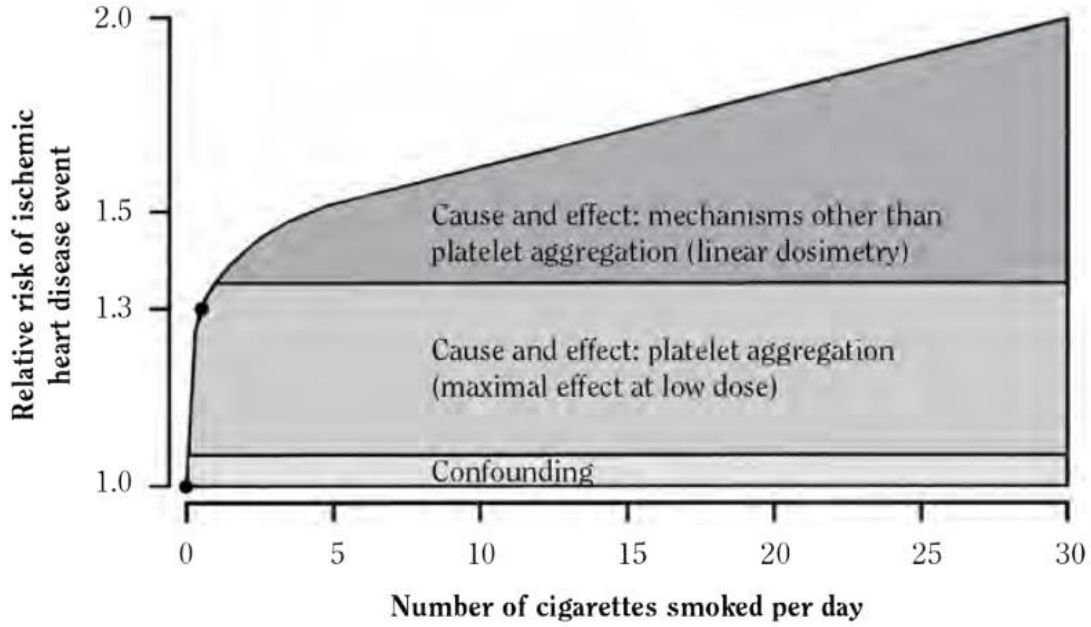
- Nicotine has some deleterious effects on the cardiovascular system. Reduction in nicotine will result in reduced effects.
- Reduction in CPD will lower exposure to toxicants in smoke which will consequentially lower CVD.
- Cessation (with NRT) has been shown to reduce the risk of and occurrence of CVD.

Joel (Joel *et al*. 2012 [pg 95]) did recognize the potential effect of VLNC on platelets and suggested that prospective studies following VLNC smokers are needed to understand these findings. The Surgeon General has reviewed the effects of cigarettes smoking on CVD (Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, and Office on Smoking and Health 2010 [pg91]) Multiple factors produced in the blood and released from the vasculature determine the likelihood of a clinically significant thrombosis. Cigarette smoke and components of the smoke stimulate formation or activity of factors that favor the development of thrombosis. The implications of the hypercoagulable state are observed both in the epidemiology of active and involuntary smoking-related cardiovascular events and in the rapid rate of decline in the major component of excess risk for those events after smoking cessation. A hypercoagulable state can result in acute myocardial infarction (MI) in persons who have less severe underlying coronary disease, so smokers who stop smoking have

a better prognosis than do nonsmokers after MI. A more gradual decline of residual risk may reflect resolution of smoking-induced vascular injury, which in turn stimulates platelet activation.

Law and Wald (2003) [pg96] conducted a meta-analysis of five large studies of smoking and coronary heart disease (CHD). They demonstrated a nonlinear dose-response relationship between the number of cigarettes smoked per day and the relative risk of disease (Figure VII.A-9). The researchers suggested that the effect of cigarette smoking on risk of CHD may have a low threshold and that the dose-response characteristics of the risk relationship are less steep at higher doses. This hypothesis was used to explain the seeming anomaly of a high RR of CHD associated with relatively low exposure to secondhand smoke. The researchers assigned a steep dose-effect due to platelet aggregation at low CPD and presumably low nicotine (ETS exposure) followed by effects from other causes. It is clear that platelet activation is part of the cardiovascular disease process, but it is unclear if VLNC will have an effect on cardiovascular disease. The effect may be overwhelmed by the beneficial effects of reduced nicotine and cigarette consumption. Quest cigarettes were marketed for almost 10 years. A search of the literature did not reveal a single citation correlating Quest or VLNC cigarettes with CVD or a thrombosis (except Girdhar *et al*. 2008, *Nicotine & Tobacco Research* [pg 93]). A review of the serious adverse events associated with VLN™ and SPECTRUM did not reveal any CVD events attributed to VLNC cigarettes.

Figure VII.A-9. Relative risk of ischemic heart disease event as a function of CPD (From Law and Wald 2003 [pg96])

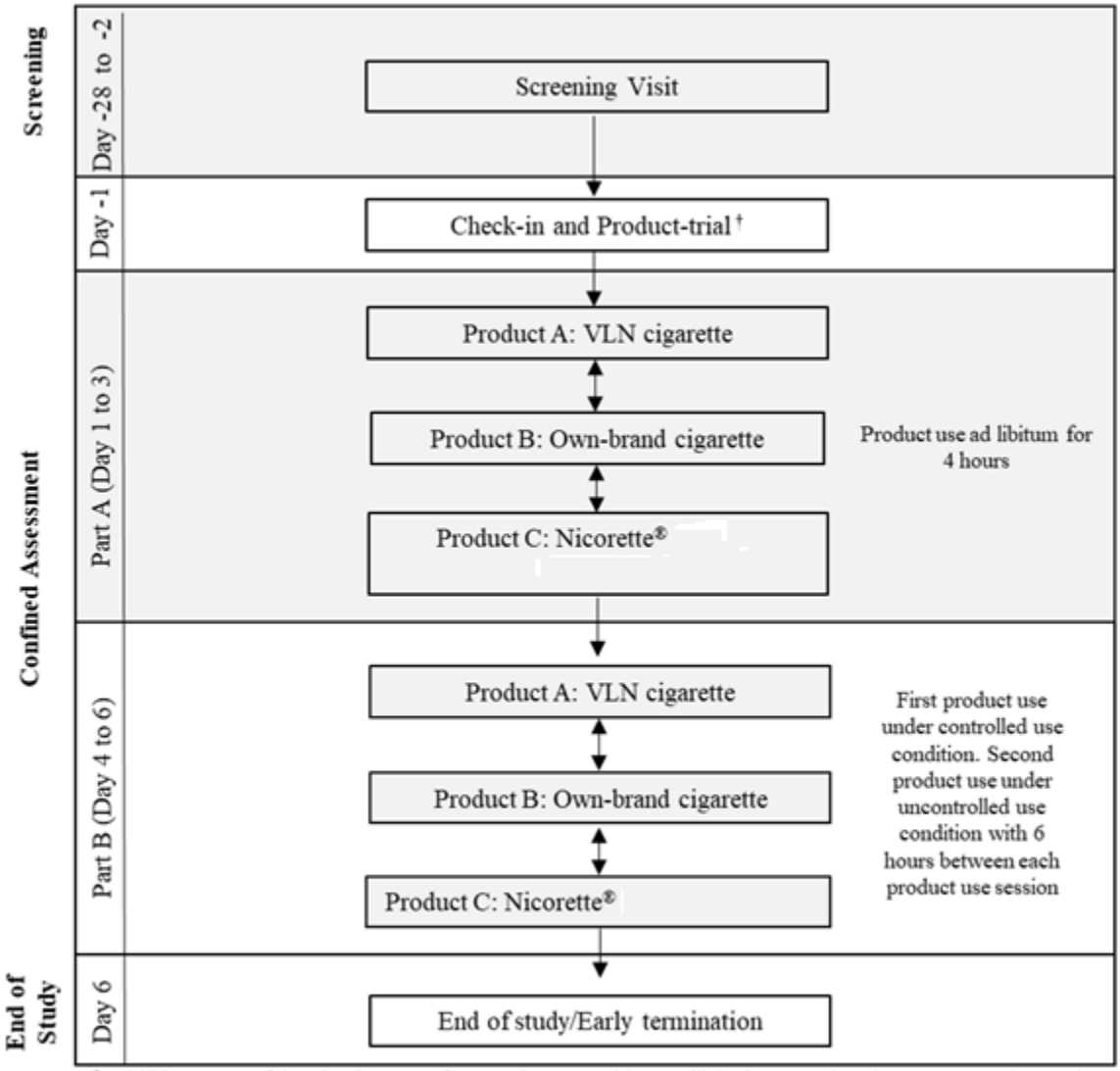


B. Abuse Liability

1. Background

Two separate abuse liability studies were conducted on VLN™ King (Altasciences 2018 [pg89]) and VLN™ Menthol King (Altasciences 2019 [pg89]). Briefly, subjects smoked their own brand, VLN™, or used nicotine gum under controlled and uncontrolled smoking conditions. Plasma nicotine levels were measured also. Urge to smoke and pleasantness were the primary end points measured. Product use behaviors were also evaluated to determine whether smokers' product use patterns were altered when using lower nicotine products. The studies were randomized cross-over designs consistent with similar published clinical studies conducted with cigarettes, non-combustible nicotine products, or nicotine replacement therapy (Stiles *et al*. 2017 [pg 100]). The studies had two parts, an *ad libitum* use of the product over 4 hours (Part A), and a single use session under both controlled and uncontrolled smoking conditions (Part B). Figure VII.B-1., *Abuse Liability Study Design*, shows the study design. Subjects received the test product in a random order.

Figure VII.B-1. Abuse Liability Study Design



† Ad libitum use of the nicotine gum for 10 minutes. Subjects will be instructed on how to correctly use the nicotine gum using the "chew and park" method.

2. VLN™ King and VLN™ Menthol King

Overall[9], analysis of the primary endpoints of Urges to Smoke VAS $E_{max\_urge(controlled)}$ and Pleasant VAS $E_{max\_plst(controlled)}$ showed that use of own-brand cigarette under Controlled Use conditions in Part B was associated with statistically significant greater reductions in subject-

[9] See Section VIII. Scientific Studies and Analyses. D. Clinical

reported urge to smoke and greater ratings of pleasantness compared with VLN™ cigarettes and nicotine gum. VLN™ cigarettes did not differ statistically from nicotine gum on either of the primary endpoints. Analysis of PK data showed that under both controlled and Uncontrolled Use conditions, peak and overall exposure to nicotine was statistically significantly lower for VLN™ cigarette compared with own-brand cigarette and nicotine gum. Therefore, despite lower nicotine exposure, VLN™ cigarettes were considered as pleasant and were able to reduce urges to smoke similarly to nicotine gum, a currently marketed nicotine replacement therapy.

Consistent with the findings on the primary endpoints, reduction in craving a cigarette ($E_{max\_crav[controlled]}$), a subscale of the Tobacco/Nicotine Withdrawal Scale, was statistically significantly lower for VLN™ cigarette and nicotine gum compared with own-brand cigarette. However, VLN™ cigarette did not statistically differ from nicotine gum indicating similar craving suppression despite lower nicotine concentrations. These findings are generally consistent with the literature that have demonstrated acute craving suppression following smoking, regardless of nicotine content (Donny *et al*. 2007 [pg 92]). The other items in the scale, i.e., Anxious VAS, Difficulty Concentrating VAS, and Impatient VAS, did not differ between products. Results for the Tobacco/Nicotine Withdrawal VAS when subjects were permitted to use the products under uncontrolled conditions in Part B were consistent with those observed during controlled use.

In terms of overall product effects, during controlled use, VLN™ cigarette and nicotine gum were rated as being less satisfying than own-brand cigarettes. In addition, both products were associated with a lower magnitude of effects related to feeling calm or feeling more awake, feeling less hungry, helping with concentration, and wanting more of the product compared with own-brand cigarette. These results were consistent when subjects used the products under

uncontrolled conditions suggesting that regardless of use condition, VLN™ cigarettes were associated with weaker "positive" or reinforcing product effects compared with own-brand cigarettes and associated with similar reinforcing effects when compared with nicotine gum. With respect to negative effects (i.e., Sick VAS), under Controlled Use conditions, VLN™ cigarettes showed lower ratings of feeling sick compared with own-brand cigarettes and nicotine gum; however, scores on this scale were low overall compared with scores on other subscales and the same results were not observed for the Uncontrolled Use condition; therefore, these findings may not be clinically meaningful.

In Part A, when subjects were permitted to use each product *ad libitum* over a period of 4 hours and in Part B during controlled and Uncontrolled Use conditions subjects were asked to rate their preference for using each of the products again at the end of the product use session. In both Part A and Part B, mean scores on Use Product Again VAS were markedly higher for own-brand cigarette compared with VLN™ cigarettes. Furthermore, the mean score for VLN™ cigarette during Part A was consistent with subjects being "unwilling to use the product again" (i.e., < 50 points on the bipolar scale); however, scores were neutral ("do not care") following VLN™ product use in Part B and consistent with the neutral scores observed for nicotine gum.

Patterns of product use were also recorded during Part A and results show that subjects smoked a similar number of VLN™ and own-brand cigarettes but spent longer smoking each own-brand cigarette. Patterns of use were also assessed during the Uncontrolled Use condition in Part B, and subjects were found to inhale a slightly lower number of puffs when using VLN™ cigarettes as compared with own-brand cigarettes. However, there was no difference in the duration of inhalation between VLN™ and own-brand cigarettes. These findings suggest that despite the

lower nicotine content in VLN™ cigarettes, subjects were not taking longer puffs or smoking more VLN™ cigarettes to compensate.

The primary endpoints in the study showed that use of the VLN™ cigarette under single controlled product use conditions was associated with lower peak ratings of pleasantness, lower reductions in urges to smoke compared with own-brand cigarettes, and markedly lower peak nicotine exposure in a sample of adult smokers. Furthermore, despite statistically significant lower nicotine exposure compared with nicotine polacrilex gum, VLN™ cigarettes were associated with similar reductions in urges to smoke and were rated to be as pleasant as nicotine polacrilex gum. These results suggest that VLN™ cigarettes have lower abuse liability compared with own-brand cigarettes and similar abuse liability as nicotine polacrilex gum. In addition, VLN™ cigarettes showed comparable effectiveness in reducing the urge to smoke and similar reductions in craving as nicotine polacrilex gum.

C. Effect on Tobacco Use Behavior among Current Users

1. Summary

Market research (M/A/R/C Research 2018 *Qualitative...* [pg97], M/A/R/C Research 2018 *Quantitative...* [pg97]) indicates the smokers with an intent to quit are most interested in this product. Non-smokers and former smokers expressed little interest in the product. Qualitative perception studies showed interest in and understanding of the claim “95% Less Nicotine”, however many consumers could not initially understand why a reduction in nicotine would be important to them. A secondary supporting statement “Helps reduce your nicotine consumption” was developed and tested. This statement was added to the principal claim to help the consumer identify why the product was important to them.

There was significant confusion by consumers about reduced nicotine and the impact this had on the safety of the product. Most consumers believe that nicotine is the chemical responsible for the diseases of smoking (O'Brien *et al*. 2017 [pg 98]). A statement was added to the pact:

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

Abuse liability studies (Altasciences 2018 [pg89] and Altasciences 2019 [pg89]) with VLN™ demonstrate that the cigarette has a very low abuse potential, less than or equal to nicotine gum. A significant amount of research has been performed on various subsets of the potential user population. Adolescent smokers found SPECTRUM (VLN™) to be less satisfying. Animal studies suggest that adolescents may be less sensitive to the reinforcing effects of low levels of nicotine. There is no data to suggest that nicotine reduction will lead to compensatory smoking in adolescents. It has been postulated that reducing the level of nicotine in cigarettes to a non-addicting level will prevent adolescence from becoming addicted to smoking and will make it easier for them to quit (Food and Drug Administration 2018 [pg93]).

Based on the published studies, it appears that smokers will gradually reduce their cigarette consumption. The amount of reduction will depend on their compliance with smoking only VLN™ cigarettes. This holds true for daily and nondaily smokers. Over time the smokers urge to smoke, and cravings seem to go down and dependence seems to be reduced.

There appears to be a sex difference in how smokers respond to the reinforcing effects of nicotine. Females have reduced sensitivity to nicotine reinforcement and reward. Females seem to report greater behavior dependence than males. This suggests that positive and negative affect that smokers experience may be different between males and females and that they might respond slightly different while using the product.

One-third of all smokers are now nondaily intermittent smokers. These smokers respond to VLN™ just like daily smokers. Switching to VLN™ caused a substantial smoking reduction but did not seem to increase abstinence.

Normal and slow nicotine metabolizers have the same smoking topography and plasma nicotine levels. Normal metabolizers reported greater reductions in craving and withdrawal than slow metabolizers.

Compliance has been raised as a potential issue in the clinical studies. In almost all studies the subjects appeared to "cheat" to some degree. In the studies, subjects were switched to VLNC cigarettes. Even when the subjects "cheated", they experienced a reduction in CPD and biomarkers of exposure. This should not be an issue with VLN™ once it is approved for sale. Consumers will make a free will choice to use the product. It is expected that they will co-use the product with NRT and conventional cigarettes. If so motivated, each consumer will develop their own plan that helps them meet their individual goals. Dual use with NRT appears to aid abstinence.

Co-use of alcohol, cannabis and opioids does not appear to affect the reduction in CPD or dependence associated with VLN™.

There are a number of sensitive populations that could possibly respond differently to VLN™. SPECTRUM (VLN™) did not affect psychiatric symptom levels in schizophrenics. In a preliminary study, people with affective disorders smoked VLN™ like normal smokers. VLN™ did not worsen depressive symptoms in depressed individuals. There was minimal evidence that people with chronic health conditions responded differently to VLN™.

In summary, there is no expectation that VLN™ will be abused by smokers. The level of nicotine is at the minimally addictive or non-addictive level. The product does not appear to be attractive to non-users (specifically legal age to 25-year-olds) or former smokers. If people initiate with VLN™, it should be easier for them to stop. There may be subtle differences in how smokers respond to VLN™, but there is no evidence that any sub-group will be harmed or will not benefit from the reduced levels of nicotine in the product. It should be noted that Quest VLNC cigarettes were marketed from 2002 to 2009 without significant problems.

2. Reduced Cigarette Consumption

Smokers who use VLN™ gradually reduce their cigarette consumption. In the largest (1250 subjects) and longest duration (20 weeks) there was a reduction of 50% (Hatsukami *et al*. 2018 [pg 94]). There are a number of factors that affect the data:

- Duration of use
- Immediate vs. progressive switch to low nicotine
- Some studies selected subjects with a desire to quit while others did not
- Some studies use baseline while others use a comparator product for comparisons
- Comparator product could be usual brand or a “normal” nicotine product like the SPECTRUM 15.8 mg nicotine

The longer smokers use the product, the more that their CPD seems to go down. Smokers who are progressively migrated from a high nicotine to low nicotine cigarette seemed to compensate during the transition and don't necessarily get the same benefit as immediate switchers (which will be the case with VLN™). Table VII.C-1., *Summary of CPD Data*, is a summary of CPD from studies ranging from 1 day to 20 weeks of use. Figure VII.C-1 shows a plot of the CPD vs. days of use. Three studies did not show any reduction in CPD. The dotted line is the trendline. This graph shows that as duration of use increased, CPD reduction increases. Most studies were conducted for 6-weeks. The range of responses after 6-weeks of use was a reduction of 11 to 46% with an average of 30%. By 20 weeks, Hatsukami (Hatsukami *et al*. 2018 [pg 94]) reported a 50% reduction (Figure VII.C-2). These studies demonstrate that use of VLN™ is likely to result in a reduction in cigarette consumption**.** These results hold true when the subjects smoked their own brand or normal nicotine content cigarettes (usually SPECTRUM 15.8 mg nicotine /cigarette). That is, these findings are not limited to just research cigarettes. It is also important to note that VLN™ smokers do not compensate by smoking more cigarettes or smoking the cigarette more intensely by increasing the size or duration of the puffs. In almost all of the clinical studies, non-compliance (smoking non-study cigarettes) was detected. Even in cases where usual brand cigarettes were smoked in conjunction with VLNC cigarettes, CPD went down and more importantly biomarkers of exposure went down. Under normal use conditions, consumers will make decisions about how and when they choose to use VLN™ cigarettes. The benefit the smoker gets will be directly related to how compliant they are with their individual smoking plan.

Table VII.C-1. Summary of CPD data.

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	CPD (% Reduction)	Reference
X-22	6-weeks	A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of X-22 as a smoking cessation aid.	232	From 19.7 to 16.7 at 6-weeks (~15%)	22nd Century Group 2011 [pg89]
Quest 3	6-weeks	Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation.	165	From 21 to 12* at 6-weeks (~43%)	Hatsukami *et al*. 2010 [pg94]
SPECTRUM	6-weeks	Randomized trial of reduced-nicotine standards for cigarettes.	840	From 22 to 15* at 6-weeks (~32%)	Donny *et al*. 2015 [pg 92]
Quest 3	35-days	A randomized controlled trial of progressively reduced nicotine content cigarettes on smoking behaviors, biomarkers of exposure, and subjective ratings.	168	NC in CPD after progressively reducing nicotine over 35 days (10 days on Quest 3)	Mercincavage *et al*. 2016 [pg 97]
SPECTRUM	10-weeks	Nondaily smokers' changes in cigarette consumption with very low -nicotine -content cigarettes a randomized double-blind clinical trial.	238	51 % decrease in CPD after 10 weeks	Shiffman *et al*. 2018 [pg 100]
SPECTRUM	8-weeks	Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial.	136	From 19 to 13* at 12-weeks (~50%) (Total cig consumption was unaffected)	Hatsukami *et al*. 2017 [pg 94]
Magic	12-weeks	Abrupt nicotine reduction as an endgame policy: A randomized trial.	33	From 12 to 9* at 8-weeks (~32%)	Walker *et al*. 2014 [pg 101]
SPECTRUM	6-weeks	Evaluation of a reduced nicotine product standard: Moderating	717	CPD reduced from 14.5 to 7.8 after 6 weeks in cannabis users (46%);	Pacek *et al*. 2016 [pg 98]

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	CPD (% Reduction)	Reference
		effects of and impact on cannabis use.		CPD reduced from 15.6 to 9.5 in non-cannabis users (39%)	
SPECTRUM	6-weeks	Effects of 6-week use of reduced-nicotine content cigarettes in smokers with and without elevated depressive symptoms.	717	CPD reduced from 15.5 to 9.1 (41%) in normal smokers	Tidey *et al*. 2017 [pg 100]
Quest 3 and Xodus	6-weeks	Reduced nicotine content cigarettes and nicotine patch.	219	From 19.5 to 14* at 6-weeks (~28%)	Hatsukami *et al*. 2013 [pg 94]
Quest 3	7-days	Reduced nicotine cigarettes: Smoking behavior and biomarkers of exposure in smokers not intending to quit.	72	From 20.0 to 20.3 after 1 week of Quest 3 (0%)	Hammond and O'Connor 2014 [pg 94]
Quest 3	9-days	Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine.	68	2.7 CPD difference after 10 days	Donny and Jones 2009 [pg 92]
Quest and Xodus	6-weeks	Sex differences in response to reduced nicotine content cigarettes.	235	From 22 to 19 in ♂ and 17.6 to 14 in ♀ after 6 weeks* (♂14%, ♀20%)	Vogel *et al*. 2014 [pg 101]
Quest 3	7-days	Mouth-level intake of benzo[a]pyrene from reduced nicotine cigarettes.	72	Progressive reduction with Quest 1, 2, &3. CPD from 14.8 to 15.0 after 7-days (0%)	Ding *et al*. 2014 [pg 92]
SPECTRUM	Single sessions and 1-week	Dose-response effects of spectrum research cigarettes.	51	CPD from 15 to 9 over 7 days* (40%)	Hatsukami *et al*. 2013 [pg 94]
Quest 3	11-days	Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days.	30	CPD reduced from 14.2 to 7.3 after 9 days* (51%)	Rupprecht *et al*. 2017 [pg 99]; Donny *et al*. 2007 [pg 92]
Quest	1-day	Effects of low nicotine content cigarettes on smoke intake.	16	CPD reduced from 11.9 to 10.4* after 1 day (13%)	Rose and Behm 2004 [pg 99]
SPECTRUM	6-weeks	Cigarette nicotine content as a moderator of the relationship	717	CPD from 21.4 to 14.2 (34%)	Robinson *et al*. 2017 [pg 99]

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	CPD (% Reduction)	Reference
		between negative effect and smoking.			
SPECTRUM	6-weeks	Estimation of compliance with exclusive smoking of very low nicotine content cigarettes using plasma cotinine.	100	CPD from 22.2 to 19.8 after 6 weeks following progressive reduction in nicotine (11%)	Foulds *et al*. 2018 [pg 93]
SPECTRUM	20-weeks	Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial.	1250	CPD from 18.6 to 8 after 20 weeks (57%)*	Hatsukami *et al*. 2018 [pg 94]

*Values not reported in original publication. Values extracted from figures in the publication.

Figure VII.C-1. Summary of CPD (dotted line is linear trendline).

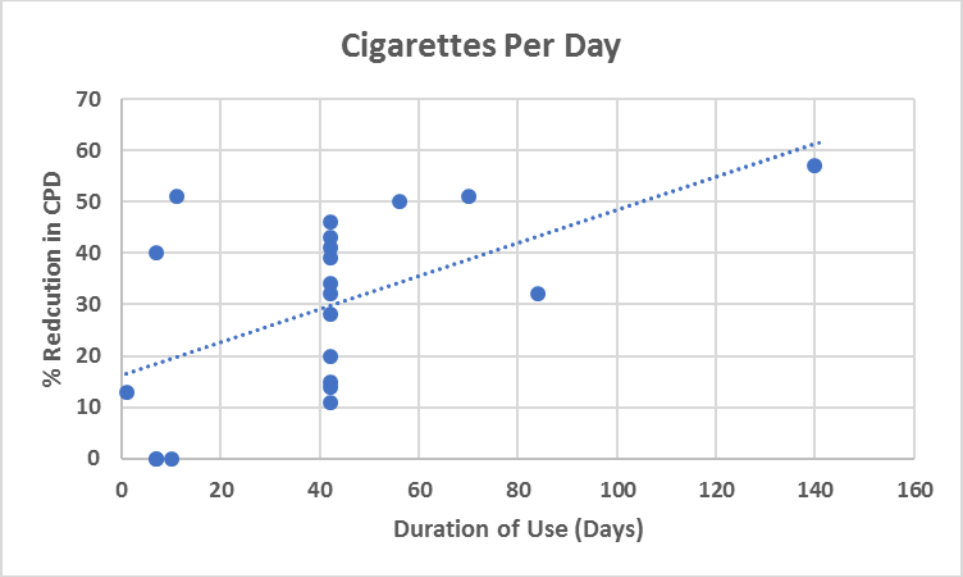
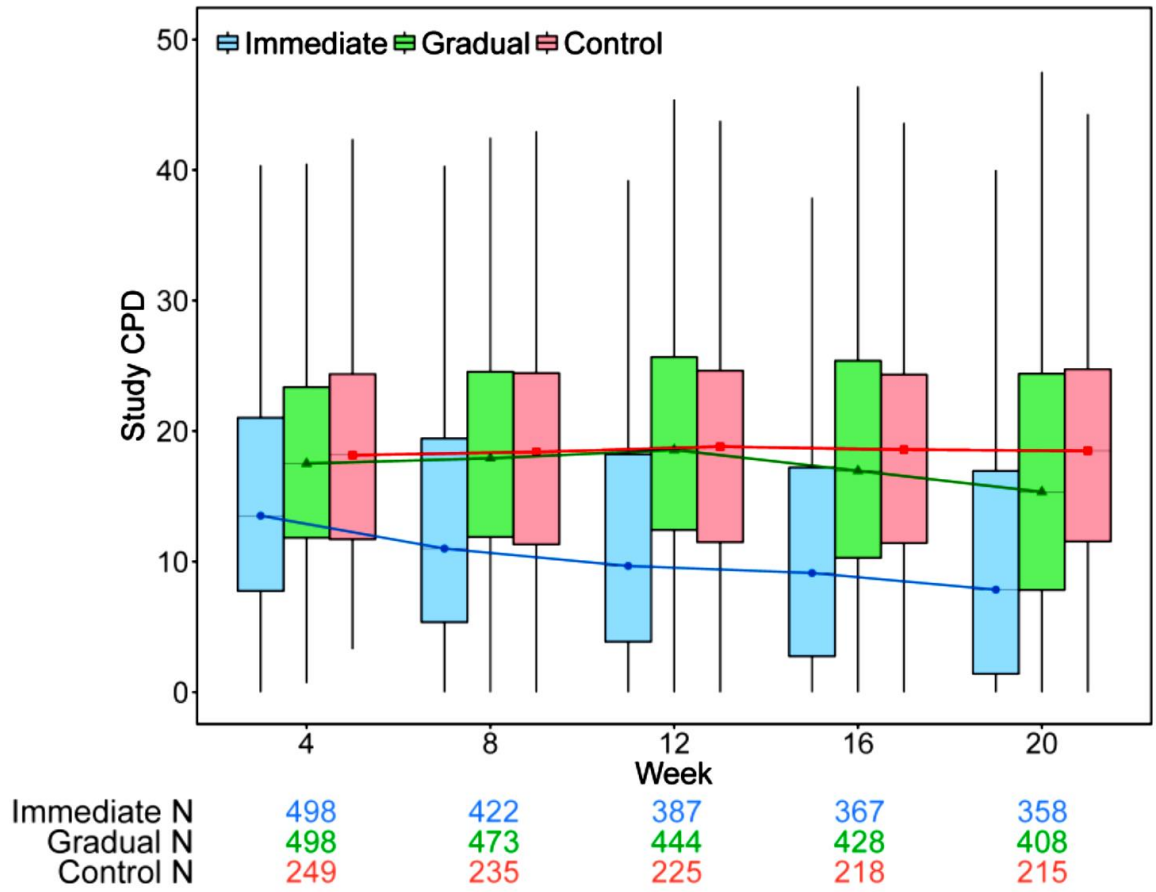


Figure VII.C-2. CPD (Subjects were immediately switched to VLN™ or gradually migrated using SPECTRUM cigarettes) (From Hatsukami *et al*. 2018 [pg 94]).



3. Smoking Urges and Cravings

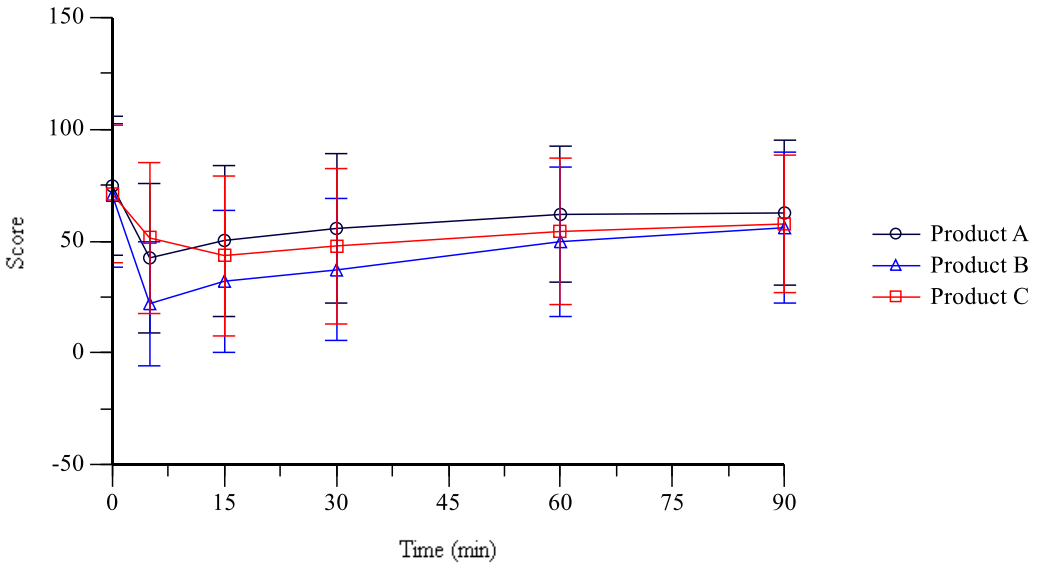
Smoking urge was measured in the abuse liability study after smoking a single cigarette under controlled and uncontrolled smoking conditions[10]. The Tobacco/Nicotine Withdrawal Questionnaire was administered as 100-point visual analogue scale (VAS). The VAS was anchored with "Not at All" on the left and "Extremely" on the right. The questionnaire items included "Urges to Smoke" and "Craving a Cigarette."

[10] See Section VIII.D. Clinical Studies.

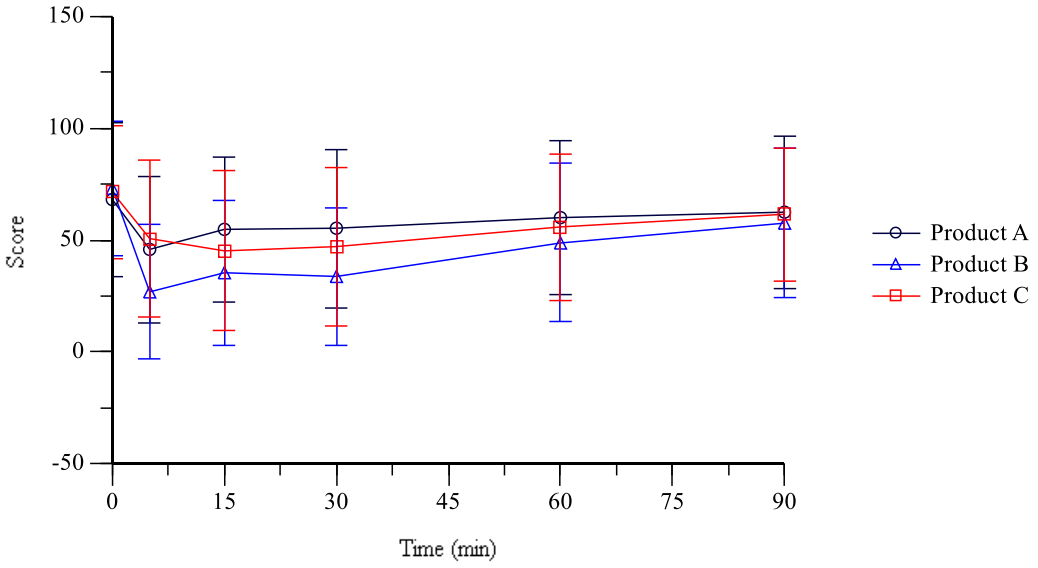
There was a statistical difference in urge and craving when comparing usual brand to VLN™ but no difference between VLN™ and gum. Usual brand appeared initially to suppress the urge to smoke and craving slightly more than VLN™ or nicotine gum (Figure VII.C-3) There were no differences between the controlled and uncontrolled smoking. These results show that VLN™ reduces the urge and craving but not quite to the level of usual brand.

Figure VII.C-3. Mean tobacco/nicotine withdrawal questionnaire responses following product administration (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

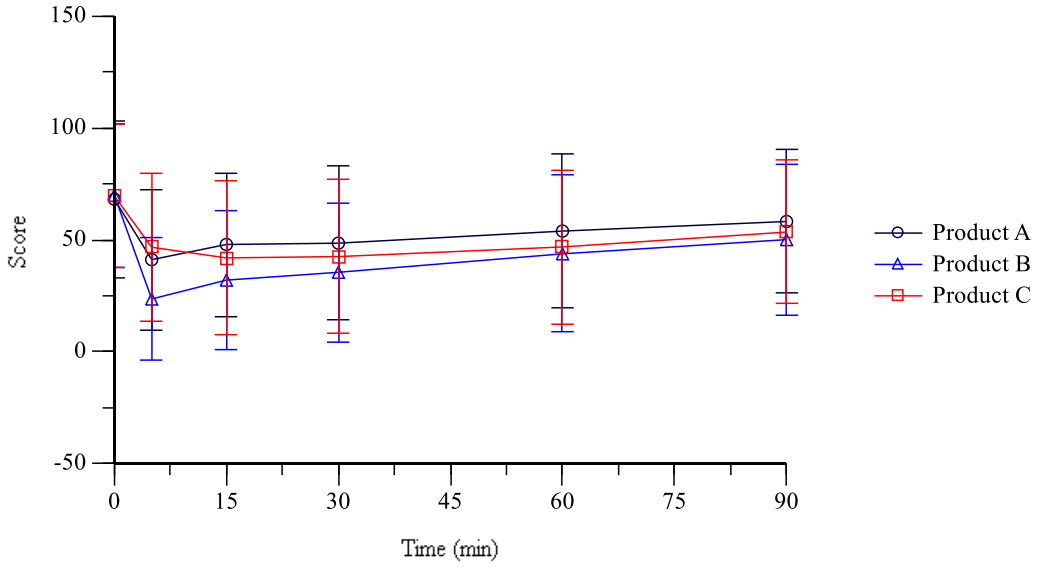
Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Craving



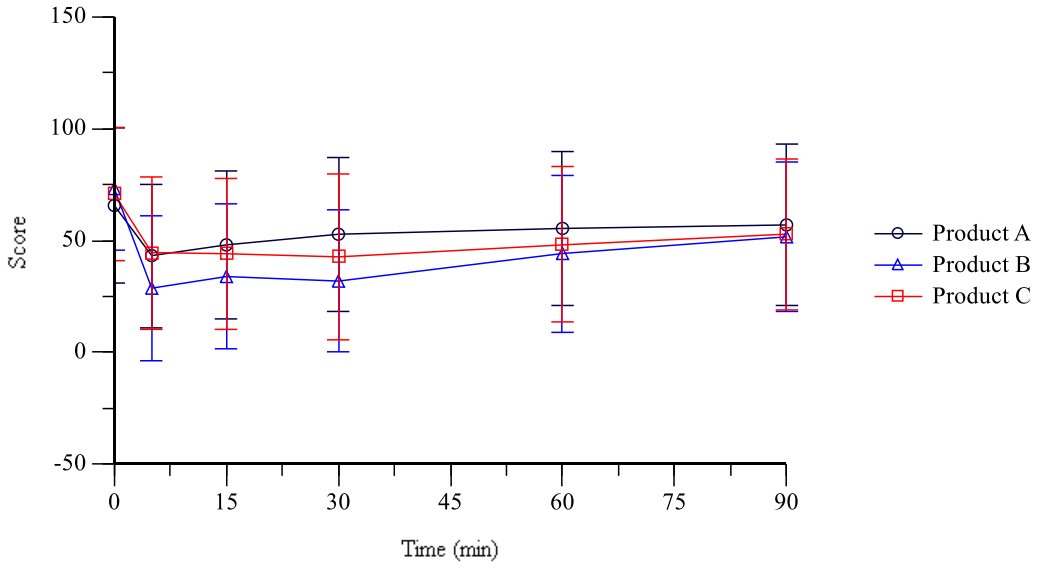
Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Craving



Condition=Controlled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Urges



Condition=Uncontrolled Use, Questionnaire=Tobacco/Nicotine Withdrawal, Question=Urges



Craving can also been measured by the Questionnaire of Smoking Urges (QSU; (Tiffany and Drobes 1991 [pg 101])). This is a 32-item self-reported measure, which was later shortened and

validated as a 10-item measure (Brief Questionnaire of Smoking Urges [QSU-Brief]; (Cox *et al*. 2001 [pg 91]). The QSU-Brief was developed in order to provide a quick, reliable, and valid measure of craving to be used in both laboratory and clinical settings. Factor analyses revealed that a two-factor solution best described the item structure of the QSU-Brief across conditions. Factor 1 items reflected a strong desire and intention to smoke (urge to smoke), with smoking perceived as rewarding for active smokers. Factor 2 items represented an anticipation of relief from negative affect with an urgent desire to smoke. The findings were consistent with the expressions of craving found in the 32-item version of the QSU (Tiffany and Drobes 1991 [pg 101]). There are 10 questions in the QSU-Brief and the subjects are instructed to respond to statements using a 100-point scale ranging from strongly disagree to strongly agree (0 to 100). The questions are listed below. Questions 1, 3, 6, 7, and 10 make up Factor 1 (F1) and Questions 2, 4, 5, 8, and 9 make up Factor 2 (F2). A higher number on Factor 1 indicates a strong urge to smoke. A higher number on Factor 2 implies anticipation of relief from withdrawal associated with abstinence.

1. I have a desire for a cigarette right now
2. Nothing would be better than smoking a cigarette right now.
3. If it were possible, I probably would smoke now.
4. I could control things better right now if I could smoke.
5. All I want right now is a cigarette.
6. I have an urge for a cigarette.
7. A cigarette would taste good now.
8. I would do almost anything for a cigarette now.
9. Smoking would make me less depressed.
10. I am going to smoke as soon as possible.

In the QSU, the subject is asked how they feel "right now." In the studies comparisons are made to usual brand or normal nicotine content cigarettes. Table VII.C-2., *Summary of Studies Reporting Effects on Smoking Urge or Craving,* summarizes the results of studies that reported QSU, smoking urge or craving. VLNC cigarettes generally were able to reduce the urge to smoke in a

manner similar to usual brand or NNC. That is, the craving reduction from VLNC was just as or almost as good as conventional cigarettes. Hatsukami (Hatsukami *et al*. 2018 [pg 94]) measured QSU over time in the 20 week study. Interestingly, the QSU Factor 1 for usual brand gradually decreased over the study. QSU Factor 1 for SPECTRUM (VLN™) deceased to a greater degree indicating that continual long-term use of VLN™ will result in a decreased urge to smoke.

Figure VII.C-4. QSU factor 1 results (From Hatsukami *et al*. 2018 [pg 94]).

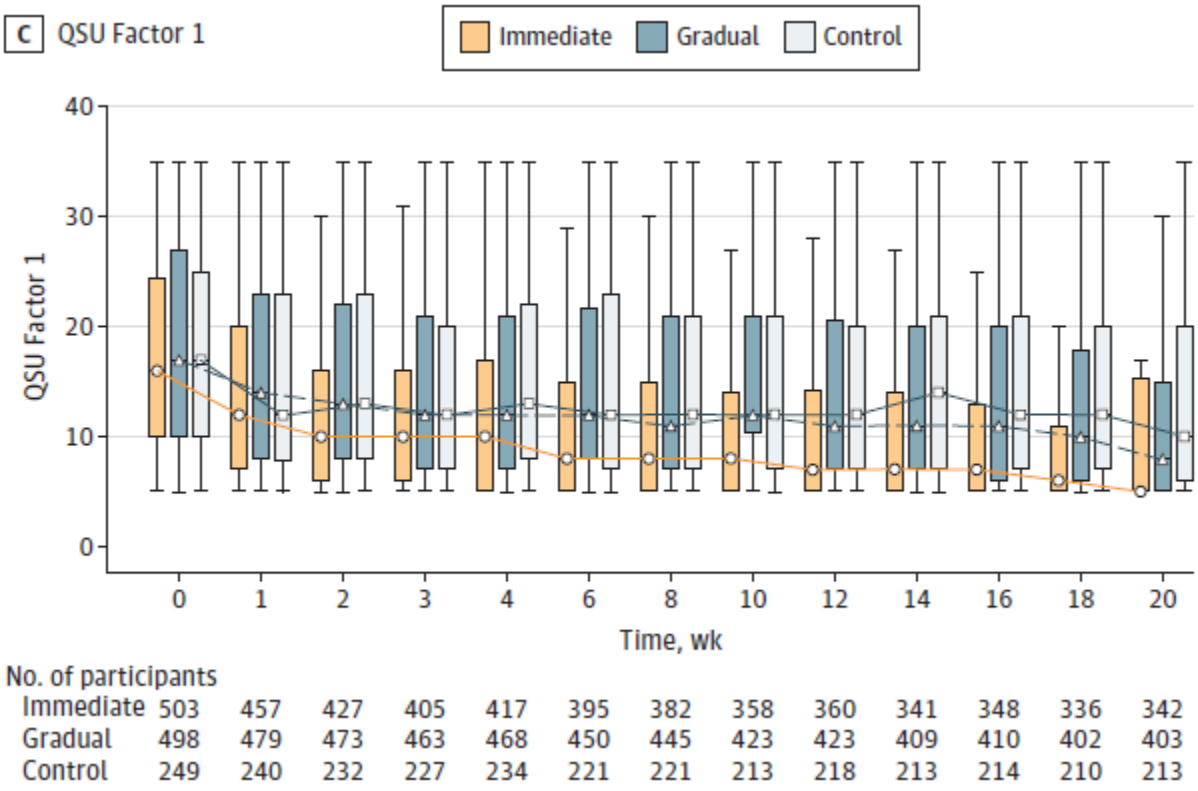


Table VII.C-2. Summary of studies reporting effects on smoking urge or craving.

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Results	Reference
VLN™	Single sessions	Evaluation of the Abuse Liability of Very Low Nicotine Cigarettes	55	No Change in craving or urge when compared to UB	Altasciences 2018 [pg89]

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Results	Reference
VLN™ Menthol	Single sessions	Evaluation of the Abuse Liability of Menthol Very Low Nicotine Cigarettes	60	No Change in craving or urge when compared to UB	Altasciences 2019 [pg89]
Quest 3	6-weeks	Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation.	165	Decreased Craving	Hatsukami *et al.* 2010 [pg 94]
SPECTRUM	6-weeks	Randomized trial of Reduced-Nicotine Standards for Cigarettes.	840	NC QSU F1 ⇓ 38% QSU F2 compared to usual brand.	Donny *et al*. 2015 [pg92]
Quest 3	Single session	Transient Compensatory Smoking in Response to Placebo Cigarettes.	83	No difference in craving reduction compared to Quest 1 after single use.	MacQueen *et al*. 2012 [pg 97]
Quest 3	Single Session	The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers.	27	⇓31% in ♂; ⇓60% in ♀* QSU F1 when compared to nicotine lozenge.	Barrett and Darredeau 2012 [pg 90]
SPECTRUM	Single session	Response to varying the nicotine content of cigarettes in vulnerable populations: An initial experimental examination of acute effects.	26	No difference in QSU F1 or 2 after acute use compared to NNC.	Higgins *et al*. 2017 *Psychopharmacology* [pg 95]
Quest 3	Single session	Alcohol-induced increases in smoking behavior for nicotinized and denicotinized cigarettes in men and women.	42	Alcohol increased desire to smoke; Quest 3 cigarettes did not affect urge.	King *et al*. 2009 [pg 95]
Magic	12-weeks	Abrupt nicotine reduction as an endgame policy: A randomized trial.	33	NC in craving after 6 weeks with use of non-study cigarettes; Reduction in craving after 12 weeks.	Walker *et al*. 2014 [pg 101]
SPECTRUM	6-weeks	Evaluation of a reduced nicotine product standard: Moderating effects of and impact on cannabis use.	717	Cannabis use moderated QSU-F1; Cannabis users exhibited greater decreases in QSU than non-users.	Pacek *et al*. 2016 [pg 98]
Quest 3	2-weeks	Treating smokers before the quit date: Can nicotine patches and	98	⇓58% QSU after 2 weeks. Use of patch	Rezaishiraz *et al*. 2007 [pg 99]

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Results	Reference
		denicotinized cigarettes reduce cravings?		and Quest 3 resulted in ⇓ 21%. *	
SPECTRUM	6-weeks	Effects of 6-week use of reduced-nicotine content cigarettes in smokers with and without elevated depressive symptoms.	717	QSU Factor 1 reduced when compared to NNC with no difference between depressive smokers and non-depressive smokers. QSU factor 2 more decreased in depressive than non-depressive smokers	Tidey *et al*. 2017 [pg 100]
Quest 3	7-days	Reduced nicotine cigarettes: Smoking behavior and biomarkers of exposure in smokers not intending to quit.	72	No difference from usual brand in QSU F1 or F2	Hammond and O'Connor 2014 [pg94]
SPECTRUM	Single session	Reduced-nicotine cigarettes in young smokers: Impact of nicotine metabolism on nicotine dose effects.	46	Smoking reduced craving. There was no difference between normal brand and SPECTRUM.	Faulkner *et al*. 2017 [pg 93]
Ultratech (<0.06 mg Nicotine)	Single session	Pharmacodynamic effects of new de-nicotinized cigarettes.	20	No difference from NNC in QSU.	Pickworth *et al*. 1999 [pg 98]
Quest and Xodus	6-weeks	Sex differences in response to reduced nicotine content cigarettes.	235	No difference in craving for ♂; decrease in craving ♀ when compared to nicotine patch	Vogel *et al*. 2014 [pg 101]
Xodus	9-weeks	Complementing the standard multicomponent treatment for smokers with denicotinized cigaret tes: A randomized trial.	200	⇓ Urge to smoke in first week of abstinence when compared to NRT	McRobbie *et al*. 2016 [pg 97]
SPECTRUM	Single sessions and 1-week	Dose-response effects of spectrum research cigarettes.	51	mCEQ Craving reduction 67% as good as usual brand	Hatsukami *et al*. 2013 [pg 94]
Ultratech (0.07 mg Nicotine)	Single session	Experimental evidence for a causal relationship between smoking lapse and relapse.	87	Ultratech craving 33% of NNC	Juliano *et al*. 2006 [pg 95]
Quest 3	Single session	Decreasing nicotine content reduces subjective and	8	No change in craving after single use.	Penetar *et al*. 2014 [pg 98]

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Results	Reference
		physiological effects of smoking.			
Quest 3	Single session	Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers.	28	Urge to smoke QSU F1 was similar between own brand and Quest as was craving.	Cobb *et al*. 2010 [pg 91]
Ultratech	Single sessions	Placebo cigarettes in a spaced smoking paradigm.	8	NNC ⇓ QSU Factor 1 54%, Ultratech ⇓ 38% NNC ⇓ QSU Factor 2 54% Ultratech ⇓ 51% 5 minutes after smoking	Eid *et al*. 2005 [pg 92]
Quest	Single sessions	Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls.	56	No difference in QSU between Quest and usual brand	Tidey *et al*. 2013 [pg 100]
SPECTRUM	Single sessions	Adolescent smokers' response to reducing the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations.	50	NNC ⇓ QSU Factor 1 49%, SPECTRUM ⇓ 31% NNC ⇓ QSU Factor 2 47% SPECTRUM ⇓ 36% 5 minutes after smoking	Cassidy *et al*. 2018, *Drug and Alcohol Dependence* [pg 91]
Quest 3	11-days	Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days.	30	No difference in QSU F1 after 11 days compared to Quest 1.	Rupprecht *et al*. 2017 [pg 99]; Donny *et al*. 2007 [pg 92]
Quest	Single sessions	Effects of low nicotine content cigarettes on smoke intake.	16	No difference in craving reduction from NNC	Rose and Behm 2004 [pg 99]
SPECTRUM	Single session	Sex differences in tobacco withdrawal and responses to smoking reduced-nicotine cigarettes in young smokers.	46	NNC ⇓ Craving 21%♀, SPECTRUM ⇓ 20% NNC ⇓ Craving 29%♂ SPECTRUM ⇓ 18%	Faulkner *et al*. 2017 [pg 93]
SPECTRUM	Single sessions	Response to reduced nicotine content cigarette	169	Craving reduction = 4.82 for NNC, 3.65	Higgins *et al*. 2018

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Results	Reference
		among smokers differing in tobacco dependence severity.		for SPECTRUM; No difference in QSU F! when compared to NNC	[pg95])
SPECTRUM	Single sessions	Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction.	169	No difference in desire to smoke compared to NNC	Higgins *et al*. 2017 *JAMA* [pg 95]
SPECTRUM	20-weeks	Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial.	1250	⇓ 52% QSU F1 when compared to NNC	Hatsukami *et al*. 2018 [pg 94]
SPECTRUM	Single Sessions	Preliminary Validity of the Modified Cigarette Evaluation Questionnaire in Predicting the Reinforcing Effects of Cigarettes That Vary in Nicotine Content	26	No difference in craving reduction when compared to NNC	Arger *et al*. 2017 [pg 89]
Quest	Single Sessions	The influence of nicotine dose and nicotine dose expectancy on the cognitive and subjective effects of cigarette smoking.	148	Smoking urged reduced more by NNC than Quest 3	Juliano *et al*. 2011 [pg 95]

*Values not reported in original publication. Values extracted from figures in the publication.

4. Adolescents

There are concerns that reduced nicotine cigarettes might be more appealing to youth than normal nicotine cigarettes, and/or might lead to compensatory smoking in youth, which could unintentionally create increased risk for smoking initiation and progression in youth. There are few studies of VLNC cigarettes in adolescents. Animal studies using self-administration models where rats are given the opportunity to make a response to obtain an infusion of nicotine have been used to study the impact on nicotine reinforcement without the societal or social reinforcers for smoking. The pre-clinical study that most directly addresses the question of how smoking naïve individuals might respond to a nicotine reduction policy was conducted by Smith, Tracy *et al*. (2014) [pg100]. In this study, one group of rats ("Acquirers") was given the opportunity to acquire self-administration at one of three low nicotine doses (3.75, 7.5, 15 ug/kg/infusion) or saline. This group might be thought of as analogous to smoking-naïve individuals who try smoking very low nicotine content (VLNC) cigarettes for the first-time. Another group of rats ("Currents") had started self-administration at a higher dose of nicotine (60 ug/kg/infusion) before experiencing a reduction in nicotine to the same three low doses of nicotine or saline. This group might be thought of as analogous to current smokers who have a history of smoking normal nicotine content (NNC) cigarettes and then experienced a reduction in nicotine content by switching to VLNC cigarettes. This study provides the opportunity to compare rates of low-dose nicotine self-administration between those who do and do not have a history of self-administering a higher dose of nicotine and can provide information about how nicotine reduction is likely to impact individuals who do and do not have a history of smoking NNC

cigarettes. The rates of self-administration were similar (i.e., not significantly different) for Acquirers and Currents for two of the nicotine doses (15 and 3.75 ug/kg/infusion) and saline. However, at one dose of nicotine (7.5 ug/kg infusion), Currents responded at a higher rate and earned more infusions than Acquirers, suggesting that their experience self-administering a higher nicotine dose may have increased sensitivity to low nicotine doses. These data suggest that individuals who initiate smoking following nicotine reduction are likely to be *less* sensitive to reinforcement by VLNCs than current smokers.

The Tracy Smith et al. study (Smith, Tracy *et al*. 2014 [pg100]) used adult rats. Published studies have shown that adolescent rats may self-administer nicotine at a *higher* rate than adults (Levin *et al*. 2003 [pg96], 2007 [pg96], 2011 [pg96]). Schassburger *et al*. (2016) [pg 99] compared male and female adolescent and adult rats and nicotine self-administration initiation of three nicotine doses (3, 10, 30 ug/kg/infusion). Both adolescent and adult rats failed to acquire self-administration of the lowest dose of nicotine (3 ug/kg/infusion). Both adolescent and adult rats acquired self-administration of the highest dose of nicotine tested (30 ug/kg/infusion), and rates of self-administration at this dose were similar between the two groups. However, the middle dose of nicotine (10 ug/kg/inf) produced acquisition of nicotine self-administration by the adult rats (i.e., it was above threshold for reinforcement), but not by the adolescent rats. These data suggest that nicotine doses that are below threshold for smoking initiation in adults are also likely to be below threshold for smoking initiation in adolescents.

Cassidy *et al*. (2018) [pg91] investigated the effect of various nicotine yield SPECTRUM cigarettes in adolescent daily smokers (age 15-19) on craving, withdrawal, and positive and negative affect pre- and post- smoking. Adolescent smokers rated the lowest nicotine level (0.4

mg/g) as less satisfying than the highest nicotine level (15.8 mg/g) cigarette (differences between other doses were not significant). One of the lower doses of nicotine (1.3 mg/g) content cigarettes was rated as less aversive compared with the highest nicotine dose (15.8 mg/g); yet the highest versus the lowest (15.8 vs. 0.4 mg/g) doses did not differ in aversiveness. All of the research cigarettes, including the lowest nicotine content (0.4 mg/g) cigarette, significantly reduced abstinence-induced withdrawal symptoms, negative affect, and craving in the laboratory. The amount of reduction in withdrawal symptoms and negative affect from smoking did not differ by nicotine content. However, for craving specifically, the highest nicotine content cigarette (15.8 mg/g) reduced abstinence-induced craving to a greater extent than the two lowest nicotine contents (1.3 mg/g and 0.4 mg/g). The authors concluded that the lower nicotine content cigarettes may have a reduced abuse liability.

Kassel *et al*. (2007) [pg95] measured smoking topography in adolescent smokers (15 to 18 years-old) comparing de-nicotinized cigarettes to high nicotine yield cigarettes. Adolescents took more puffs per de-nicotinized cigarette than the high yield cigarette, but total puff volume did not differ between the two cigarette types. There was a non-significant increase in CO. The Cassidy study (Cassidy *et al*. 2018, *Drug and Alcohol Dependence* [pg 91]) did not demonstrate any CO boost in adolescents. Studies in adults do not demonstrate compensation with VLNC cigarettes. There is no data to suggest that adolescents will compensate either.

These results suggest that adolescents (based on rat studies) are likely to be less sensitive to reinforcement from very low levels of nicotine compared with adults, and that nicotine doses below the threshold for reinforcement in current adult smokers are also likely to be below threshold for adolescents initiating smoking for the first time. Research with human adolescents

complement the preclinical findings, in that adolescents found research cigarettes with the lowest nicotine content (0.4 mg/g) less reinforcing than cigarettes with the highest nicotine content. There is no data to indicate that nicotine reduction leads to compensatory smoking in adolescent smokers. Thus, the concerns that reduced nicotine cigarettes might be more appealing to youth than normal nicotine cigarettes, and/or might lead to compensatory smoking in youth appear to be unfounded. It should be noted that if adolescents initiate with VLNC cigarettes, theoretically, they will not become addicted to the nicotine and therefore it may be easier for them to quit.

5. Sex Differences

A review by Perkins (Perkins 2009 [pg 98]), describes studies that demonstrate females have reduced sensitivity to nicotine reinforcement and reward. Females, compared to males, show less differential self-administration of nicotine versus placebo when administered via nasal spray, less choice of nicotine spray over placebo, and less response to pre-treatment with nicotine (especially at lower doses of nicotine). Perkins (Perkins *et al.* 2002 [pg 98]) administered subjects' own brand cigarettes and cigarettes with a nicotine yield of 0.1 mg (Carlton Ultra Light) in a double-blind manner to participants. They observed a dose by sex interaction where females experienced less difference in subjective responses (e.g., satisfaction, perceived nicotine content, similarity to own brand) between the two different yield cigarettes compared to males. Furthermore, when given the opportunity to work for additional puffs on a cigarette, no differences were observed between the two yield cigarettes for females while males earned more puffs on the higher dose cigarette.

Studies have also shown that females appear more sensitive to visual, olfactory and taste cues than males ((Evans *et al*. 2006 [pg 92]); (Perkins *et al*. 2001 [pg 98]); (Perkins *et al*. 2002 [pg 98]). Females also report greater behavioral dependence ((Bohadana *et al*. 2003 [pg 90]); (Perkins 2009 [pg 98]) and less nicotine dependence with cigarettes. Nicotine may be more reinforcing in men than in women. (Perkins *et al*. 2002 [pg 98])

The apparent sex differences in response to nicotine has led to studies investigating how males and females may respond to VLNC cigarettes.

- Withdrawal decreased less after Quest 3 in men than in women. Negative affect decreased from pre-smoking baseline following the Quest 1 vs Quest 3. There was marginally a greater effect in men. (Perkins and Karelitz 2015 [pg 98])
- The combination of Quest 3 and nicotine patches was more effective in alleviating withdrawal symptoms in males than females. Females were more likely to quit smoking than males when assigned to either of the conditions that incorporated the Quest cigarettes; however, males were more likely to quit smoking in the nicotine patch alone condition than females (Vogel *et al*. 2014 [pg 101]).
- Faulkner (Faulkner *et al*. 2018 [pg 93]) investigated the acute effects of SPECTRUM cigarettes in young adults (mean age = 22). Men but not women reported greater craving reduction, perceived nicotine content, and cigarette liking with increasing nicotine dose. Women reported greater psychological withdrawal, greater sedation, and a trend toward greater craving than men during abstinence. Women also reported greater reductions in psychological withdrawal and sedation than men due to smoking, with no effect of nicotine dose. Men reported greater reductions in craving after smoking cigarettes delivering ≥ 0.231 mg nicotine than after smoking cigarettes delivering ≤ 0.231 mg nicotine. Women reported no effect of nicotine dose on cigarette liking, cigarette disliking, and perceived nicotine content, whereas men reported greater liking, less disliking, and greater perceived nicotine content as the nicotine content of the cigarette increased. These results suggest that there is a sex difference in response to SPECTRUM cigarettes.

6. Nondaily Smokers

Shiffmann (Shiffman *et al*. 2018 [pg 100]) evaluated the effect of SPECTRUM cigarettes in 238 nondaily intermittent smokers. These smokers benefited from using the VLNC cigarettes reducing their cigarette consumption 1.6 CPD (from a baseline value of about 3 CPD) over the 10-week study when compared to NNC cigarettes. They also reduced the number of days per week they smoked. Based on their smoking rate, these smokers would be considered minimally addicted. Use of VLNC cigarettes did not impact abstinence.

7. Normal and Slow Metabolizers

Nicotine is metabolized primarily by the hepatic cytochrome P450 enzyme CYP2A6, with approximately 80% of nicotine converted to cotinine (COT), which is further metabolized by the same enzyme to 3'-hydroxycotinine (3HC) (Benowitz 2009 [pg 90]). There is wide individual variability in the clearance of nicotine, due both to genetic variation and environmental and hormonal factors. The ratio of 3HC/COT, also called the nicotine metabolite ratio (NMR), is a phenotypic biomarker that can be measured in plasma, urine, and saliva and is correlated with the rate of nicotine clearance (Dempsey *et al*. 2004 [pg 91]). The NMR accounts for both genetic and non-genetic influences of CYP2A6 activity, is reproducible within subjects, and independent of the time since last cigarette smoked (Lea *et al*. 2006 [pg 96]; Mooney *et al*. 2008 [pg 97]; St Helen *et al*. 2012 [pg 100]).

The rate of nicotine metabolism is an important determinant of tobacco and nicotine dependence. Faster nicotine metabolism is associated with greater dependence/higher tobacco consumption and lower rates of quitting without pharmacotherapy and with transdermal nicotine patch compared to slower metabolizers (Rubinstein *et al*. 2008 [pg 99]; Lerman *et al*.

2006 [pg 96]; Patterson *et al*. 2008 [pg 98]; Schassburger *et al*. 2016 [pg 99]; Schnoll *et al*. 2009 [pg 99]; Ho *et al*. 2009 [pg 95]; Lerman *et al*. 2015 [pg 96]). Fast metabolizers experience more severe craving/withdrawal and are more likely to smoke to relieve such symptoms, i.e. for negative reinforcement (Lerman *et al*. 2006 [pg 96]; Sofuoglu *et al*. 2012 [pg 100]). This is supported by findings showing that smokers with higher NMR experience more anxiety, insomnia, difficulty concentrating, anger and impatience during abstinence (Rubinstein *et al*. 2008 [pg 99]; Kaufmann *et al*. 2015 [pg 95]). Another possible mechanism is that positive reinforcement may be greater among faster metabolizers.

Because of the apparent differences in nicotine metabolism, it is of interest to investigate how nicotine metabolism affects the response to VLNC cigarettes. There were no differences between SPECTRUM and the preferred-brand cigarette, in puff count, average volume, intensity, or duration in slow and normal metabolizers. Moreover, there were no differences between normal and slow metabolizers on any such measures when smoking reduced-nicotine cigarettes or the preferred-brand cigarette. There were no differences between the plasma nicotine levels of slow and normal metabolizers after smoking SPECTRUM or preferred-brand cigarettes. All cigarettes equally alleviated craving, withdrawal, and negative affect, but normal metabolizers reported greater reductions of craving and withdrawal than slow metabolizers. All cigarettes increased positive effect and decreases negative effect. The findings suggest that smoking-induced relief of craving and withdrawal reflects primarily non-nicotine effects in slow metabolizers but depends on nicotine dose in normal metabolizers. By contrast, relief of withdrawal-related attentional deficits and cigarette ratings depend on nicotine dose regardless of metabolizer status (Faulkner *et al*. 2017 [pg 93]).

8. Dual Use

i. Conventional Cigarettes

In just about all of the clinical studies with VLNC cigarettes, compliance was an issue. Various studies go so far as to track and report the non-study cigarette usage. It is clear from biomarkers of exposure that subjects in the studies may have been getting nicotine from non-study cigarettes. Nardone (Nardone *et al*. 2016 [pg 97]) conducted a secondary analysis of a large multi-site study to measure non-compliance biochemically with urine cotinine and total nicotine equivalents. The authors were able to detect more cases of non-compliance than self-reported. Despite the non-compliance the smokers reduced their intake of nicotine by an average of 60%. The clinical studies go to extremes to make sure that subjects use only the research cigarettes. This is important to show the clinical significance of the study results. Upon authorization to sell VLN™ cigarettes, smokers will be making a purchase choice to reduce their nicotine and possibly their cigarette consumption. The body of research suggests that if they are motivated to quit, VLN™ cigarettes could help them reduce their dependence on nicotine. The studies show that even if the VLN™ smoker is dual using conventional cigarettes, they will likely benefit from using the VLN™.

ii. NRT

VLNC have low positive and high negative subjective effects (Donny and Jones 2009 [pg 92]). NRT can decrease the number of VLNC cigarettes smoked. NRT also have the effect of decreasing the total volume of smoke inhaled but had little effect on the subjective effects of VLNC cigarettes (Donny and Jones 2009 [pg 92]). Hatsukami (Hatsukami *et al*. 2013 [pg 94]) observed that NRT led to lower rates of smoking VLNC cigarettes. The combination of VLNC cigarettes and NRT was

associated with less withdrawal severity. The combination of VLNC cigarettes and NRT was more effective in reducing use of VLNC cigarettes and withdrawal symptoms in males than females, whereas females were equally responsive to VLNC cigarettes with and without NRT (Vogel *et al*. 2014 [pg 101]). Dual use of VLNC cigarettes with NRT increases abstinence in people motivated to quit (Becker *et al*. 2008 [pg 90]; McRobbie *et al*. 2016 [pg 97]; Walker *et al*. 2012 [pg 101] ; Vector Tobacco Inc. 2006 [pg 101]; Hatsukami *et al*. 2017 [pg 94]; Hatsukami *et al*. 2013 [pg 94]). There is limited evidence that suggests VLNC cigarettes with NRT increases smoking abstinence in smokers not motivated to quit (Benowitz *et al*. 2012 [pg 90]; Walker *et al*. 2014 [pg 101]; Shiffman *et al*. 2018 [pg 100]).

9. Co-Use

i. Alcohol

Alcohol and tobacco co-use is widespread (Falk *et al*. 2008 [pg93]), and the use of both substances may be causally linked (Dermody and Donny 2014 [pg92]). Barrett *et al*. (2006 [pg89]) published a study on the effect of VLNC cigarette use on drinking. Among college-aged men (n = 15), VLNC cigarettes decreased alcohol use during a laboratory session relative to normal nicotine content (NNC) cigarettes. The results suggested that reduced nicotine exposure in the presence of smoking-related sensorimotor cues from VLNC cigarettes may decrease alcohol intake. Dermody (Dermody *et al*. 2016 [pg 92]) investigated the effect of SPECTRUM cigarettes on alcohol usage as part of a larger multicenter trial specifically looking at daily alcohol use and binge drinking. There was no evidence of compensatory drinking in response to nicotine reduction 6 weeks or nicotine withdrawal in current drinkers expected to be at a greater risk. King *et al*. (2009) [pg 95] investigated the effect of alcohol use on smoking urges and topography after NNC (Quest

1) or VLNC (Quest 3). Alcohol increased both men's and women's smoking urge. There was no difference in response to NNC or VLNC cigarettes. There are no clear indications that VLNC cigarettes will increase alcohol drinking.

ii. Cannabis

Results suggest that SPECTRUM use is unlikely to alter current rates of cannabis use (Pacek *et al*. 2016 [pg 98]). SPECTRUM use did not impact the prevalence or frequency of cannabis use. Cannabis use did not moderate most effects of SPECTRUM use. Parker (Parker *et al*. 2018 [pg 98]) conducted a secondary analysis of the large Donny study (Donny *et al*. 2015 [pg 92]). Participants positive for cannabis use were selected. Cannabis use status did not moderate the effects of nicotine dose on concurrent choice testing, subjective effects of VLNC, or smoking topography. After adjusting for sociodemographic characteristics, cannabis users had higher ratings on smoking satisfaction, enjoyment of respiratory tract sensations, and craving reduction across all nicotine doses.

iii. Opioids

There were no significant differences in smoking topography after acute use of SPECTRUM cigarettes in opioid-dependent smokers. The cigarettes effectively reduced nicotine withdrawal (Higgins *et al*. 2017 [pg 95]).

10. Sensitive Populations

i. Schizophrenia

Schizophrenia is associated with a threefold higher prevalence of cigarette smoking compared to the general population (Hennekens *et al*. 2005 [pg 94]). One factor that may contribute to smoking persistence in this population is the disruptive effects of abstinence on

neurocognitive functioning (Wing *et al*. 2012 [pg 101]). Cognitive deficits are considered a core feature of schizophrenia (Heinrichs and Zakzanis 1998 [pg 94]) and are associated with poor functional outcomes in these patients (Green 1996 [pg 93]). Experimental studies have found that smoking abstinence impairs attention and spatial working memory performance in smokers with schizophrenia (SS), and smoking reinstatement reverses these impairments (George *et al*. 2002 [pg 93]; Sacco *et al*. 2005 [pg 99]). Switching to VLNC cigarettes may negatively affect cognitive performance in SS.

- Acute use of Quest 3 cigarettes does not increase the intensity of smoking in schizophrenic smokers. Schizophrenic smokers took longer puffs and had a shorter inter-puff interval but took fewer puffs overall producing no net increases (Tidey *et al*. 2016 [pg 101]).
- SS and control smokers (CS) smoked usual brand, Quest 3 while wearing two placebo patches, or Quest 3 with 2 NRT patches. The findings from this study indicate that acute use of Quest 3 cigarettes, compared to usual-brand cigarettes, negatively affected attention, inhibitory control, processing speed, and response time variability in both SS and CS, and that NRT patches reversed this impairment. As impairments in these domains are thought to have direct implications for the functional outcomes of smokers with schizophrenia (Mohamed *et al*. 2008 [pg 97]), these findings suggest the need to consider adjunctive nicotine and alternative agents for preservation of cognition in SS smokers. (AhnAllen *et al*. 2015 [pg 89])
- In a second study, Tidey evaluated the effect of SPECTRUM cigarettes along with nicotine patches in schizophrenic subjects (SS) (Tidey *et al*. 2013 [pg 100]). Smoking SPECTRUM cigarettes reduced cigarette craving, nicotine withdrawal symptoms, habit withdrawal symptoms and usual brand smoking in both SS and CS subjects alike. SPECTRUM did not affect psychiatric symptom levels in SS. Addition of nicotine patches reduced craving.

ii. Affective Disorders

Affective disorders are a set of psychiatric disorders mainly comprised of mood disorders (e.g., depressive disorders, bipolar disorder) and anxiety disorders (egg, generalized anxiety disorder, panic disorder and post-traumatic stress disorder). They are prevalent among smokers (Gaalema *et al*. 2015 [pg 93]). In the United States, 13% of smokers have a current mood disorder

and 23% have a current anxiety disorder(Lawrence *et al*. 2009 [pg96]). Smoking prevalence rates among individuals with mood disorders is 2- to 3-fold higher than those in the general population (Lasser *et al*. 2000 [pg 96]; McClave *et al*. 2010 [pg 97]; Smith, Philip *et al*. 2014 [pg100]). Smokers with affective disorders are more likely to be nicotine dependent, initiate daily smoking earlier, and smoke more cigarettes per day than those without psychiatric comorbidity (Breslau *et al* 2004 [pg 91]; Dierker and Donny 2008 [pg 92]; Goodwin *et al*. 2012 [pg 93]; Colard *et al*. 2015 [pg 91]; Lawrence *et al* 2009 [pg 96]).

Epidemiological data show that people with affective disorders are significantly less likely to quit smoking than those without current mental illness (Lasser *et al*. 2000 [pg 96]; Smith, Philip *et al*. 2014 [pg100]; Weinberger *et al*. 2012 [pg 101]). Smokers with affective disorders do not appear to differ from smokers without these disorders on readiness to quit, (Tsoh and Hall 2004 [pg 101]; Prochaska *et al*. 2004 [pg 99]; Young-Wolff *et al*. 2014 [pg 102]) nor are those with comorbid depression or anxiety disorders less likely to accept smoking cessation treatment when treatment is offered (Baron *et al*. 2013 [pg 89]; Beckham *et al*. 2013 [pg 90]; Haug *et al*. 2005 [pg 94]). Following initial withdrawal from nicotine, smokers with affective disorders experience more severe disruption than smokers without these disorders. Use of VLNC cigarettes during abstinence may help mitigate the mood-disrupting effects of initial abstinence. (Gaalema *et al*. 2015 [pg 93])

In a preliminary study in 6 subjects there were no significant differences in smoking topography after acute use of SPECTRUM cigarettes in individuals with affective disorders. The cigarettes effectively reduced nicotine withdrawal. (Higgins *et al*. 2017, *Psychopharmacology* [pg 95])

iii. Clinically Depressed

The prevalence of smoking among adults with depression is significantly higher than that of adults without a current mental health condition (40% vs. 15.5%). (Smith, Philip *et al*. 2014 [pg100]) The elevated risk of smoking among people with depression is due to both a higher likelihood of becoming tobacco dependent and a lower likelihood of smoking cessation (Smith, Philip *et al*. 2014 [pg100]; Lasser *et al*. 2000 [pg 96]). Elevated depressive symptoms in general are associated with smoking progression and persistence (Ameringer and Leventhal 2010 [pg 89]; Audrain-McGovern and Benowitz 2011 [pg 89]; Escobedo *et al*. 1998 [pg 92]; Berlin and Covey 2006 [pg 90]; Cinciripini *et al*. 2003 [pg 91]; Lukowski *et al*. 2015 [pg 96]). Barriers to cessation in smokers with elevated depressive symptoms include high levels of cigarette craving and withdrawal-related negative affect, along with beliefs that smoking improves negative affect (Leventhal *et al*. 2013 [pg 96]; Pang *et al*. 2014 [pg 98]). Although smoking reduces withdrawal-related negative affect, smoking cessation is associated with improvement, rather than worsening, in depressive symptoms over time (Taylor *et al*. 2014 [pg 100]). Since VLNC cigarettes have less nicotine and affect withdrawal it is possible that the VLNC cigarettes could worsen depression. Tidey (Tidey *et al*. 2017 [pg 100]) evaluated the effect of SPECTRUM cigarettes on subjects with depressive symptoms in a 6-week study. Use of SPECTRUM cigarettes may reduce smoking, without worsening depressive symptoms, among smokers with depressive symptoms.

iv. Chronic Health Conditions

Individuals with chronic health conditions continue smoking despite the presence smoking-related illness. Streck (Streck *et al*. 2018 [pg 100]) performed a secondary analysis on the large multi-site Donny trial (Donny *et al*. 2015 [pg 92]). Participants were categorized as having 0,

1–2, or ≥3 smoking-related chronic health conditions (i.e., chronic condition severity, CCS). Repeated-measures analysis of variance was used to examine whether CCS moderated response to cigarettes across measures of addiction potential (i.e., concurrent choice testing between nicotine dose pairs, Cigarette Purchase Task (CPT) performance, positive subjective effects), tobacco withdrawal, cigarette craving, and smoking topography. No main effects of CCS or interactions of CCS and nicotine dose were observed for concurrent choice testing, positive subjective effects, tobacco withdrawal, or smoking topography. Main effects of CCS were noted on the CPT with greater CCS being associated with less persistent demand. There was an interaction of CCS and nicotine dose on Factor 1 of the Questionnaire on Smoking Urges with the effects of dose significant only among those with 1–2 chronic conditions. There was minimal evidence that chronic condition severity affects response to reduced nicotine content cigarettes.

D. Effect on VLN™ Use Initiation among Non-Users

No studies have been conducted with VLN™ cigarettes in non-smokers. Qualitative (M/A/R/C Research 2018, *Qualitative…* [pg97]) and quantitative (M/A/R/C Research 2018 *Quantitative…* [pg97]) research using VLN™ packs and messaging indicates little or no interest in VLN™ among former smokers and non-users. As discussed elsewhere VLN™ cigarettes contain a target level of 0.5 mg nicotine per g of tobacco - 95% less nicotine than in the tobacco than conventional cigarettes. Benowitz and Henningfield (Benowitz and Henningfield, 1994 [pg 90]) hypothesized that the threshold nicotine dose for reinforcing effects, a primary indicator of addiction potential, was approximately 0.7 mg nicotine per g tobacco (~0.5 mg/ cigarette)[11]. An abuse liability study with VLN™ (Altasciences 2018 [pg89]) indicated that the plasma

[11] At that time there had been no discussion of the basis for determining the nicotine content i.e. dry weight or weight of tobacco. SPECTRUM cigarettes were reported to have 0.4 or 0.5 mg of nicotine, but no basis was given.

nicotine levels were substantially less than usual brand and even an order of magnitude less than 4 mg nicotine gum. This level is considered non- or minimally-addictive. It has been proposed that this reduction to a non- or minimally-addictive level will make it easier for smokers to quit and prevent non-smokers who initiate with VLN™ from becoming addicted (Food and Drug Administration 2018 [pg93]).

The FDA has proposed to reduce the levels of nicotine in all tobacco products (Food and Drug Administration 2018 [pg93]). Apelberg (Apelberg *et al*. 2018 [pg 89]) performed an analysis of what the public health impact would be of reducing the nicotine levels in all cigarettes in the United States under the proposed policy. Table VII.D-1., *Effects of nicotine reduction policy on tobacco related behavior*, shows the projected number of persons who would not become established smokers over time because of the policy[12]. Since a sustained decrease in rates of smoking initiation is expected, the cumulative number of persons who are dissuaded from starting to smoke continues to increase over time. Apelberg estimated that by 2060 16.0 million persons (5th to 95th percentile range, 3.9 to 31.0) who would have otherwise initiated smoking will not have started because of the policy. This number increased to 33.1 million (5th to 95th percentile range, 8.0 to 64.1) by 2100. While these projections are based on a mandated reduction in nicotine levels in all cigarettes, it is rational to expect that any non-smokers who happen to use VLN™ will not become addicted and will find it easier to quit (Food and Drug Administration 2018 [pg93]).

Further analysis suggests that those reported values were on a wet weight basis. Since tobacco can contain varying amounts so water, it is important to consider the values only on a dry basis.

[12] The policy assumes that the nicotine level in **all** cigarettes will be reduced to the same non- or minimally-addictive level.

Table VII.D-1. Effects of nicotine reduction policy on tobacco related behavior (From Apelberg *et al*. 2018 [pg 89])

Table 1. Effects of a Nicotine-Reduction Policy on Tobacco-Related Behavior, According to Projections Provided by Eight Experts.*

Behavioral Projection and Timing after Implementation	Minimum	Percentile					Maximum
		5th	25th	50th	75th	95th	
		percentage of persons					
Current smokers who quit smoking as a result of the policy							
Women and girls							
Yr 1	4.0	7.5	11.0	19.0	30.0	40.0	50.0
≥Yr 2	3.9	5.5	8.4	13.5	23.8	37.5	45.0
Men and boys							
Yr 1	4.0	7.5	12.0	21.0	30.0	40.0	50.0
≥Yr 2	3.9	5.5	9.4	15.0	26.3	37.5	45.0
Current smokers who quit and switch to non-combusted tobacco products							
Women and girls							
Yr 1	15.0	20.0	25.0	35.0	52.5	72.5	80.0
≥Yr 2	15.0	20.0	27.5	37.5	52.5	72.5	80.0
Men and boys							
Yr 1 and yr 2	15.0	20.0	30.0	40.0	55.0	72.5	80.0
Continuing smokers among both sexes who become dual-product users							
Yr 1	20.0	30.0	42.5	60.0	75.0	82.5	92.5
≥Yr 2	8.8	12.5	20.0	30.0	57.5	70.0	75.0
Reduction in annual rate of smoking initiation among both sexes							
Yr 1	10.0	15.0	25.0	50.0	65.0	80.0	90.0
≥Yr 2	10.0	15.0	25.0	50.0	70.0	80.0	90.0
Would-be smokers among both sexes who instead initiate use of noncombusted tobacco products							
Yr 1 and yr 2	10.0	15.0	22.5	37.5	62.5	77.5	85.0

* In each category, the values indicate the median of eight responses. Experts were able to make separate estimates of the effects of the policy on men and women. If the values are the same for men and women or for the two time periods, the values have been merged into combined categories. For comparison purposes, the population-weighted average annual rate of smoking cessation was 3.7% among women and 3.3% among men in the baseline scenario (all years). At the beginning of the policy scenario (year 2020), the prevalence of dual use of cigarettes and noncombusted tobacco products was 2.3% among both men and women. At baseline, the initiation rates for cigarette smoking varied according to age, peaking at the age of 16 years among girls (at 2.5% per year) and at the age of 17 years among boys (at 3.4% per year). The initiation rates for noncombusted tobacco products also varied according to age, peaking at the age of 16 years among girls (at 1.8% per year) and at the age of 17 years among boys (at 5.5% per year).

E. Effect of Marketing on Consumer Understanding and Perceptions

A consumer perception study was performed in ~28,000 subjects. Subjects were asked about their perceptions on the health risks of nicotine containing products. They also were asked about their perceptions of the risk of addiction of the same products. The subjects were then shown VLN™ pack concepts. Marlboro Gold and a VLN™ pack without claims were also tested.

The subjects were then asked the same perception questions. At different times during the study participants were asked what their purchase and use intent would be for the products. Never smokers and former smokers demonstrated no interest in the products. Youth, as indicated by a proxy group of legal smoking age to 25 sub-group of never smokers were also not interested in the product. Purchase and use intent were universally rated as "Definitely would not." Analysis of perceptions of health risks and risk of addiction of the nicotine containing products before and after exposure to the product concepts indicated that the subjects understood the risks of VLN™ cigarettes as well as the comparator nicotine containing products. Exposure to the VLN™ product concept did not change the subjects' perception of the health risks of the other nicotine containing products. The subjects accurately predicted that the addiction potential of VLN™ would be less than conventional cigarettes indicating that they understood the product concept. Current smokers demonstrated an interest in purchasing and using the product. Their perceptions of the health and addiction risks of nicotine containing products as well as VLN™ was consistently slightly lower than the perceptions of never and former smokers. Smokers with an intent to quit had slightly higher perceptions of health and addiction risks of the comparator products and VLN™ when compared to smokers with no intent to quit. Smokers with an intent to quit had higher purchase and use intents than smokers with no intent to quit.

The overall results of the study suggest that participants understood the modified exposure message and perceived that VLN™ poses some health and addiction risks. Furthermore, the results demonstrate that the VLN™ modified exposure message did not mislead participants into believing that VLN™ is less harmful or that VLN™ poses less health risk as compared to other tobacco products.

F. Effect on the Population as a Whole

A model (Certara USA, Inc. 2018 [pg91]) was developed to evaluate the impact of introduction of VLN™ on the population. Market research shows that VLN™ cigarettes are not attractive to new potential smokers considering initiating or former smokers relapsing to conventional cigarette smoking. VLN™ has 95% less nicotine than conventional cigarettes on the market. VLN™ is just as hazardous as conventional cigarettes. The risks of consuming VLN™ cigarettes and risks of being exposed to environmental tobacco smoke from VLN™ are expected to be the same as conventional cigarettes. That is, the risks are the same irrespective of product, VLN™ or conventional cigarette, and therefore do not need to be considered since the concentrations of toxicants will be the same for the smoker or the person exposed to environmental tobacco smoke. For this reason, effects of environmental tobacco smoke are not considered in the model, and different relative risks for VLN™ are considered only in the sensitivity analysis.

The target market for VLN™ is current smokers who wish to reduce their nicotine consumption. Possible consequences of switching to VLN™ cigarettes include reduced cigarette consumption and increased quitting, with corresponding gradual reductions in mortality rates. The model predicts the effect of introducing VLN™ in 2020 on mortality over the period 2015 to 2100[13]. The model outputs included cumulative avoided cigarette-attributable deaths and life-years gained after switching to VLN™ cigarettes. Avoided cigarette-attributable deaths were calculated as the difference in cigarette-attributable deaths with VLN™ cigarettes versus without

[13] The model predicts smoking rate declines and mortality from 2015 to 2020 using published data. The effect of introducing VLN™ in 2020 is then incorporated into the model's assumptions.

VLN™ cigarettes, where cigarette-attributable deaths arise from the increase in risk of death for smokers relative to never-smokers. Likewise, life-years gained in each year are calculated as the difference in the annual predicted adult population with versus without VLN™ cigarettes. Under a base-case scenario, the model predicts conventional cigarette smokers who switch to VLN™ cigarettes will avoid about 340,000 smoking-attributable deaths and add about 8.05 million life-years to their lives by the year 2100 (cumulative). Younger adults will experience the greatest long-term benefits, due to their longer opportunity to switch to VLN cigarettes. Under a best-case scenario there will be almost 1 million avoided smoking attributable deaths and almost 19 million life years gained.

For comparison purposes, a scenario was constructed assuming a 2020 mandated reduction in cigarette nicotine to minimally addictive levels, similar to the recent Apelberg publication (Apelberg *et al*. 2018 [pg 89]). In this scenario, the model predicts about 8.2 million avoided smoking-attributable deaths and 150 million life-years gained by 2100, similar to Apelberg's base-case (8.5 million and 134 million respectively).

G. Label Development and Claims Support

1. Label development

The process of developing the label and various statements about the product was a reiterative process. This process is outlined in the qualitative studies (M/A/R/C Research 2018 *Qualitative* [pg97]). Initially, the Company was interested in investigating reduced exposure and reduced risk statements. Since the Company decided not to pursue reduced risk claims, only a discussion of the reduced exposure statements follows. The following items were considered in the process:

- The statements could not be false or misleading;
- The statements could not be stated or implied health claims;
- The statements could not state or imply safety;
- The statements needed to be truthful;
- The statements needed to be supported by research.

While going through the process additional considerations were developed:

- The statements needed to be understandable;
- The statements needed to be simple, clear, and concise;
- The product needed to be positioned so that non-smokers or new smokers were not attracted to the product;
- The consumer needed guidance in understanding why reduced nicotine was important to them;
- There was confusion on the role of nicotine in disease and a statement was needed to make sure that the consumer understood that reduced nicotine did not mean a safer cigarette.

In Phase I of the qualitative research (M/A/R/C Research 2018 *Qualitative...* [pg97]), a focus group was shown reduced exposure and reduced risk statements. The primary claim that was being tested was "Very Low Nicotine." The tested reduced exposure statements are listed in Table VII.G-1., *Statements Tested in Phase I Focus Group*:

Table VII.G-1. Statements Tested in Phase I Focus Group

Phase	Phase I
Claim Type	Reduced Exposure

Primary Claim	VERY LOW NICOTINE	VERY LOW NICOTINE	VERY LOW NICOTINE	VERY LOW NICOTINE	VERY LOW NICOTINE
Secondary (Comparative) Claim	PARE Cigarettes Contain 95% Less Nicotine Than Leading Brands*	Made with PARE'S Patented Reduced-Nicotine Tobacco*	PARE Cigarettes Contain 95% Less Nicotine Than Leading Brands*	This product is made with tobacco containing very low levels of nicotine, an addictive chemical*	Nicotine is an addictive chemical. PARE Cigarettes Contain Less Than 5% of the Nicotine of Leading Brands*
	**Approximately 95% less nicotine in tobacco and smoke compared to the top 3 selling brands.*	**The tobacco in PARE Cigarettes Contains Less Than 5% of the nicotine of the three leading US cigarettes.*	**Approximately 95% less nicotine in tobacco and smoke compared to the top 3 selling brands.*	**The tobacco in PARE Cigarettes Contains Less Than 5% of the nicotine of the three leading US cigarettes.*	**Compared to the top 10 best-selling brands.*
Disclaimer	The Tobacco Smoke From PARE Cigarettes is No Safer Than Smoke From Any Other Cigarette.	No cigarette is safe. Very Low Nicotine does not mean a safer cigarette.	PARE Cigarettes Are No Safer Than Any Other Cigarette.	This cigarette is not a safe alternative to traditional cigarettes.	No Cigarette is Safe. PARE Cigarettes Present The Same Health Risks as Other Cigarettes.
Back of Pack Language	PARE exposes you to significantly less nicotine, an addictive chemical.	This product contains much lower levels of nicotine, an addictive chemical. However, it is "tar," not nicotine, that causes smoking-related diseases. The "tar" produced by PARE is comparable to "tar" produced by other cigarettes.	All tobacco products contain nicotine, an addictive chemical. PARE Cigarettes give you much less nicotine than competing brands. However, smoking PARE is no safer than smoking any other cigarette.	This product contains significantly lower levels of nicotine than other cigarettes, which may help you better manage your smoking. However, it is "tar," not nicotine, that causes smoking-related diseases. The "tar" in PARE is comparable to "tar" produced by other cigarettes.	People smoke cigarettes to get nicotine, but it's the smoke or "tar" that kills smokers. Smoke from a PARE cigarette contains less nicotine than other cigarettes but it is no different from the smoke from other cigarettes. Smoking PARE cigarettes over the long-term will cause the same damage to your health as smoking any other cigarette.

Subjects were asked which set of statements they felt did the best job of communicating about VLN™ (PARE)[14] to the consumer. The subjects were then asked to "build their own" label. The highlighted boxes represent the consumer preferences.

Reactions to the product concept included:

- Respondents felt that PARE / VLN™ was intended for:
- Those trying to quit smoking or cut back
- Casual smokers
- New smokers
- Some were confused by the concept, as they did not understand why a cigarette manufacturer would try to help them quit.

[14] At this stage of development, the product was named PARE, the name used for the 2015 PMTA/MRTPA.

- Many expressed confusions as to PARE / VLN™'s intended category: is it a cigarette or is it nicotine replacement therapy?
- Initially, PARE / VLN™ was seen as "less risky" or as a "healthier alternative" to other cigarettes.
- Subsequent exposure to the product claims ultimately conveys the risk associated with using PARE / VLN™.

Key Reactions to PARE / VLN™ Claims

- Respondents liked the use of the term "95% less nicotine" as it was eye-catching to smokers and stated a compelling piece of information related to how PARE / VLN™ differed from other cigarettes.
- In general, "95% less" made more sense than stating "less than 5% of the nicotine."
- Different comparator statements were tested including:
- Approximately 95% less nicotine in tobacco and smoke compared to the top 3 selling brands.
- The tobacco in PARE Cigarettes Contains Less Than 5% of the nicotine of the three leading US cigarettes.
- Approximately 95% less nicotine in tobacco and smoke compared to the top 3 selling brands.
- The tobacco in PARE Cigarettes Contains Less Than 5% of the nicotine of the three leading US cigarettes.
- Compared to the top 10 best-selling brands.
- The preferred statement was 95% less nicotine than the leading brands. Consumers didn't necessarily know what the top selling brands were and how this related to their brand. It was felt that a broader statement was easier to understand and relate to.
- Many respondents found the statements, particularly those on the back of pack, to be too long and felt that communicating the facts in a concise manner would be more impactful.
- Several noted that references to nicotine as "addictive" is important to note, but many stated that it is a known fact, especially to smokers, and does not provide additional value. Some found the thought of being an "addict" was offensive.
- Numerous participants felt certain statements presented a contradiction by calling out PARE / VLN™'s purported benefits (e.g. contains less nicotine, helping to curb cravings), then stating that the product is no safer than any other cigarette.
- However, respondents repeatedly noted that they liked the "honesty" shown by PARE / VLN™ in calling out the fact that the product is not a safe alternative.
- Repeated mentions of the word "tar" was seen as overwhelming and unnecessary.

In Phase II focus groups, the primary claims "Very Low Nicotine" and "95% Less Nicotine" were tested along with different comparative claims and supporting information (Table VII.G-2). Subjects were asked which set of statements they felt did the best job of communicating about VLN™ (PARE)[15] to the consumer. The subjects were then asked to "build their own" label. The highlighted boxes represent the consumer preferences.

Table VII.G-2. Statements Tested in Phase II Focus Group.

Phase	Phase II				
Claim Type	Reduced Exposure				
Primary Claim	VERY LOW NICOTINE	95% LESS NICOTINE*	VERY LOW NICOTINE*	VERY LOW NICOTINE	VERY LOW NICOTINE
Secondary (Comparative) Claim	PARE Cigarettes Contain 95% Less Nicotine Than Leading Brands*	Made with PARE'S Patented Reduced-Nicotine Tobacco	PARE Cigarettes Contain 95% Less Nicotine Than Leading Brands	Nicotine is an addictive chemical. PARE Cigarettes Contain 95% Less Nicotine Than the 3 Leading US Brands	The tobacco in PARE Cigarettes contains 95% less nicotine than the three leading US brands.
	** Compared to the top 3 selling US brands.*	**Compared to the three leading US brands.*	**Compared to the top 3 selling brands.*		
Disclaimer	The Smoke From PARE Cigarettes Is No Safer Than Smoke From Any Other Cigarette.	No cigarette is safe. Very Low Nicotine does not mean a safer cigarette.	PARE Cigarettes Are No Safer Than Any Other Cigarette.	No Cigarette Is Safe. PARE Cigarettes Present the Same Health Risks as Traditional Cigarettes.	This cigarette is not a safe alternative to traditional cigarettes
Back of Pack Language	PARE exposes you to significantly less nicotine, an addictive chemical.	This product contains much lower levels of nicotine, a chemical which can increase the urge to smoke. However, it is "tar", not nicotine, that causes smoking-related diseases. The "tar" produced by PARE	All tobacco products contain nicotine, an addictive chemical. PARE Cigarettes give you much less nicotine than competing brands. However, smoking PARE is no safer than	People smoke cigarettes for the nicotine, but it's the smoke or "tar" that kills smokers. Smoke from a PARE cigarette contains less nicotine than other cigarettes but it is no different from the smoke from other cigarettes.	This product contains significantly lower levels of nicotine than other cigarettes, which may help you better manage your smoking. However, it is the "tar" in smoke, not nicotine, that

[15] At this stage of development, the product was named PARE, the name used for the 2015 PMTA/MRTPA.

		is comparable to "tar" produced by other cigarettes.	smoking any other cigarette.	Smoking PARE cigarettes over the long-term will cause the same damage to your health as smoking any other cigarette.	causes smoking-related diseases. The "tar" in PARE is comparable to that produced by other cigarettes.

Reactions to the PARE / VLN™ Concept

- Similar to Phase I feedback, Phase I respondents believed PARE / VLN™ to be intended for:
  - Those trying to quit smoking or cut back
  - Casual smokers
  - To a lesser degree, new smokers
- The appeal to new smokers was mentioned less often in Phase 2 as compared to Phase 1.
- Many participants raised questions regarding the use of the term "genetically modified" and how it impacted the tobacco in PARE / VLN™. Several wanted to know what was "being added" to PARE / VLN™ to lower the nicotine content (a negative association).

Key Reactions to PARE / VLN™ Claims

Statements in Phase II were modified based upon feedback from Phase I.

- As seen in Phase I, statements and questions about the "tar" in cigarette smoke were frequent.
- Long-term quitters seem to be more educated about tar and, as a result, clearly understand the risks of smoking/risks associated with PARE / VLN™.
- Lack of education around the effects of tar is evident across all other groups.
- The phrase "kills smokers" elicited a strong response. This terminology is distinctly offensive to smokers.
- Smokers' aversion to this language could hinder adoption of PARE / VLN™ because the language is viewed to be harsher than what is commonly used within the market.
- Some respondents noted that this direct language is important to call out, given that smoking is perceived as being hazardous.

- Overall, recent quitters react more like current smokers in their assessment of the claims. The risk of recidivism is apparent with this group based upon their feedback.
- Respondents liked the use of the term "95% less nicotine" as it was eye-catching to smokers and stated a compelling piece of information related to how PARE / VLN™ differed from other cigarettes. In general, "95% less" is more attractive wording than the phrase "Very Low Nicotine."
- Many respondents found the statements, particularly those on the back of pack, to be too long and felt that communicating the facts in a concise manner would be more impactful.
- Several noted that references to nicotine as "addictive" is important to note, but many stated that it is a known fact, especially to smokers, and does not provide additional value.
- Respondents prefer definitive language (e.g. use the word "can" instead of "may" in phrase "may help you break that addiction."
- Numerous participants felt certain statements presented a contradiction by calling out PARE / VLN™'s purported benefits (e.g. contains less nicotine, helping to curb cravings), then stating that the product is no safer than any other cigarette. However, respondents repeatedly noted that they liked the "honesty" shown by PARE / VLN™ in calling out the fact that the product is not a safe alternative.
- Repeated mentions of the word "tar" on the Back of Pack was seen as overwhelming and unnecessary. Many stated the word should be removed.
- Opinions varied regarding comparisons of PARE / VLN™ to "top" or "leading" brands. Some liked the point of reference, while others felt it was meaningless without listing the brands.

Phase III was an in- depth interview with 50 subjects in different parts of the U.S. The primary claims "Very Low Nicotine" and "95% Less Nicotine" were tested along with different comparative claims and supporting information (Table VII.G-3). A content statement (Less than 0.6 mg nicotine per cigarette) was also tested. Subjects were asked which set of statements they felt did the best job of communicating about VLN™ (PARE)[16] to the consumer. The subjects were then asked to "build their own" label. The highlighted boxes represent the consumer preferences.

[16] At this stage of development, the product was named PARE, the name used for the 2015 PMTA/MRTPA.

Table VII.G-3. Statements Tested in Phase III In-Depth Interview.

Phase	Phase III			
Claim Type	Reduced Exposure			
Primary Claim	VERY LOW NICOTINE	VERY LOW NICOTINE	95% LESS NICOTINE*	VERY LOW NICOTINE
Secondary (Comparative) Claim	95% Less Than the Most Popular US Brands. Nicotine is an addictive chemical.	Less than 0.6 milligrams per cigarette.	Made with Very Low Nicotine Tobacco	PARE Cigarettes Contain 95% Less Nicotine Than Leading Brands.
		www.parecigarettes.com	**Compared to the three leading US brands.*	**Compared to the 3 top-selling US brands.*
Disclaimer	No Cigarette, Including PARE, Is Safe.	Long-Term Smoking of Any Cigarettes, Including PARE, Is Hazardous To Your Health.	No cigarette is safe. Very Low Nicotine does not mean a safer cigarette.	PARE Cigarettes Are No Less Toxic Than Any Other Cigarette.
Back of Pack Language	All tobacco products contain nicotine, an addictive chemical. PARE contains significantly less nicotine than other brands. However, smoking PARE is not safer than smoking other cigarettes. www.parecigarettes.com	PARE exposes you to significantly less nicotine, an addictive chemical.	Nicotine creates the urge to smoke, but the other toxic chemicals in smoke are what cause smoking-related disease and death. The toxic chemicals in PARE are comparable to those in other cigarettes.	PARE contains much less nicotine than other cigarettes, which may help you better manage your smoking. However, it is the other compounds in smoke, not nicotine, that cause smoking-related diseases. PARE contains the same harmful compounds as other cigarettes.

The 95% Less Nicotine statement was again the most popular. The 0.6 mg nicotine amount meant little without a comparison. Most consumers didn't know how much nicotine was in their cigarette. Comparisons to "Most Popular Brands" or "Leading Brands" was meaningful. Responders questioned what specific brands were being referenced. It was suggested that the comparator be dropped if the brands cannot be listed.

Reactions to the PARE / VLN™ Concept

- Phase 3 respondents indicated that PARE / VLN™ was intended for those trying to quit smoking or cut back.
- Respondents were quick to understand PARE / VLN™'s intended purpose. Casual and New smokers were mentioned less often than in Phase II.

Key Reactions to PARE / VLN™ Claims

- Use of the term "Toxic" was polarizing. Some felt it was necessary to stress the dangers of smoking, others felt it steered consumers away from the product.
- The phrase "Causes diseases and death" was also viewed as too blunt by some.
- As seen in prior rounds, "95% less nicotine" wording resonates well with respondents.
- Many suggest putting "95% less nicotine" on the top front; if Very Low Nicotine is put on the pack, it could go on the top back. Several said they would visit the website, but primarily to obtain coupons or promotional items. The "For more information" phrasing was more appealing than simply listing the website; leads them to want to learn more. Many indicated the website should be on all packs, with most preferring it on the back. Many did not immediately notice the asterisk. Once noticed, many indicated that means "fine print and you are trying to hide something." Putting the footnote on the side of the pack in very small print just reinforced this feeling. Most indicated either leave off the footnote or move it to the front or back of pack.

Phase IV was an in- depth interview with 54 subjects in Paramus, New Jersey. The primary claims "95% Less Nicotine" was tested along with supporting statements (Table VII.G-4). The goal of the research was to find out which supportive statements consumers preferred and how they interpreted the statements. Previous studies had tested various different "disclaimers." A final disclaimer was crafted to convey to the consumer that VLN™ cigarettes are not safer, less nicotine does not mean safer, and all cigarettes can cause disease and death. Subjects were asked which set of statements they felt did the best job of communicating about VLN™[17] to the consumer. The highlighted boxes represent the consumer preference.

Table VII.G-4. Statements Tested in Phase IV In-Depth Interview.

Phase	Phase IV
Claim Type	Reduced Exposure
Primary Claim	95% LESS NICOTINE

[17] At this stage of development, the product was named VLN™. Two different pack formats/color schemes were tested.

Secondary Claim	Helps reduce your urge to smoke	Helps reduce your nicotine consumption	Helps you smoke less	Helps reduce your cigarette consumption
Disclaimer	Nicotine is addictive. Less nicotine does NOT mean safer. All cigarettes can cause disease and death.			
Back of Pack Language	VLN™ smells, burns, and tastes like a conventional cigarette, but greatly reduces your nicotine consumption.			

The various secondary supporting claims resonated with consumers. They liked the 95% Less Nicotine at the top of the pack. The concept of reducing nicotine consumption was viewed as a "no-brainer" that was honest and truthful. The concept of reducing smoking urge hit home also. Helping reduce cigarette consumption also resonated with the consumers. This was what potential quitters want.

Over the course of the four qualitative research phases, the message and potential statements about the product were modified. The intent to use went from unlikely to somewhat unlikely over the development. The product's concept of reduced nicotine was difficult for smokers to understand. Pairing the reduced nicotine content statement with supporting a statement like "helps reduce your nicotine consumption" helped the consumer understand why reduced nicotine was important to them. The product concept only really appealed to smokers with an intent to quit and then only marginally. Former smokers could understand the concept but were not interested in the product. Non-smokers were not interested in the product for themselves, but many said this was the product their friends needed to help them quit.

There were some key results from the qualitative research on the principal claim statement:

1. "95% Less Nicotine" was preferred over "Very Low Nicotine", "5% of the Nicotine", or a nicotine content statement.

2. "95% Less Nicotine" was eye-catching to smokers and stated a compelling piece of information related to how VLN™ differed from other cigarettes.

3. Comparative statements for the 95% Less Nicotine to "top" or "leading" brands was liked by some but others felt it was meaningless without listing the brands. If comparative statements are used, the consumers want to know where their brand is in the mix.

Based on the qualitative research, pack statements substantially similar to those tested in Phase IV were used in the Quantitative research study (M/A/R/C Research 2018, *Quantitative...* [pg97]). Specific supporting statements (claims) were placed on the packs that related to the benefits of the product supported by the research. The Company believes that most consumers do not understand the benefit from the "95% Less Nicotine" statement alone. Many consumers falsely believe that nicotine is the cause of the diseases associated with smoking (O'Brien *et al*. 2017 [pg98]). To them a reduction in nicotine potentially signals that this product may have less risk than conventional cigarettes. Many consumers do not also understand that nicotine is the addictive component of cigarettes. The FDA has recently required nicotine addiction statements on all electronic cigarettes to inform consumers. The Company has gone to great lengths to state on the pack that nicotine is addictive, that reducing nicotine does not make the product safer, and that all cigarettes cause disease. Without knowledge or guidance, the consumers don't

understand the benefits of VLN™ cigarettes. Adding a supporting statement of why a reduction in nicotine is important to the consumer helps the consumer understand the benefits of VLN™.

2. "95% Less Nicotine"

Section 911(h)(2)(B) states that the Secretary may also require, for purposes of subparagraph (A), that the percent (or fraction) of change and identity of the reference tobacco product and a quantitative comparison of the amount of the substance claimed to be reduced shall be stated in immediate proximity to the most prominent claim. The principal reduced exposure claim for the products (VLN™ King and VLN™ Menthol King) is "95% Less Nicotine". This statement meets the requirements of Section 911(h)(2)(B). This claim is based on the nicotine content of the filler in the cigarette irrespective of the basis of comparison (per g of tobacco filer, per gram of tobacco filer calculated on a dry weight bases, or per cigarette. The target level for VLN™ Tobacco is 0.5 mg nicotine/g of tobacco filler (dry weight). Batch analysis proves that the product can be made to this target level (See Section VIII.A.1.1. Batch Analysis). 22nd Century has been producing cigarettes with this target level of nicotine since 2011. Most of these cigarettes were made under the SPECTRUM brand name for NIDA. The top 100 brands in the U.S. were identified and analyzed for nicotine in filler (See Section VIII.A.1.2. Filler Nicotine Analysis of top 100 Brands). These results demonstrated that VLN™ had a greater than a 95% reduction of nicotine in the tobacco compared to the top 100 brands representing over 80% of all cigarettes sold in the U.S. An additional analysis was performed of the top 100 brands measuring the nicotine per cigarette. The average nicotine per cigarette was 12.0 mg. VLN™ contains 0.27 mg /cigarette. This validates the claim "95% less nicotine." Because of the unique technology used to reduce nicotine and the absence of the technology in any other cigarette on the market, the

Company firmly believes that the nicotine level in VLN™ is reduced at least 95% when compared to **all** other cigarettes in the marketplace and a comparator statement such as "leading brands", "usual brand", "typical brands", or "top three brands" is not required. Making a comparison to a single brand such as the "market leader" or Marlboro Gold also is not informative to the consumer unless the consumer smokes that specific brand. There are over 1250 brands and sub-brands sold in the United States. Making a statement comparing against Marlboro for example, as the leading brand family, does not inform the consumer which specific Marlboro cigarette is being used for comparison. The product could be a king or a 100. It could be a menthol or regular. It could be a hard pack or soft pack. Of the top 100 brands sold in the U.S., 36 are branded Marlboro, 11 are Camel's, 10 are Pall Mall and 7 are Newport's. Making a comparative statement to any one of these brands or to the group will not guide the consumer. In addition, a statement comparing to a specific brand family may raise questions in the consumers mind when a new sub-brand is launched.

Section 911(h)(2)(A) states that the Secretary may require for the marketing of a product under this subsection that a claim comparing the tobacco product to 1 or more other commercially marketed tobacco products shall compare the tobacco product to a commercially marketed tobacco product that is representative of that type of tobacco product on the market (for example the average value of the top 3 brands of an established regular tobacco product). Table VII.G-5 shows the comparison of VLN™ to the top 3 brands. Irrespective of the basis of comparison (/g filler, /g filler dry weight, /cigarette, or /cigarette in smoke) the reduction in the amount of reduction in nicotine in VLN™ is consistently greater than 95% less than the competitors. Table VII.G-6 shows the same comparison to the top 3 **King** size brands. Irrespective

of the basis of comparison (/g filler, /g filler dry weight, /cigarette, or /cigarette in smoke) the reduction in the amount of reduction in nicotine in VLN™ is consistently greater than 95% less than the competitors.

Table VII.G-5. Comparison of VLN™ to Top 3 Brands.

Product	**Market Position**	**Nicotine (mg/g tobacco filler)**	**Nicotine (mg/g tobacco filler; Dry Weight Basis)**	**Nicotine (mg/cigarette)**	**Nicotine (mg/cigarette (Smokie yield)**
Marlboro Gold King	1	15.9	18.2	10.3	0.67
Marlboro Red King	2	15.8	17.4	11.0	0.956
Newport Menthol Green 100	3	18.9	21.4	14.8	1.50
Average Top 3		**16.9**	**19**	**12.0**	**1.042**
VLN™ King		0.41	0.47	0.27	0.03
VLN™ Menthol King		0.41	0.47	0.27	0.03
Average VLN™		**0.41**	**0.47**	**0.27**	**0.03**
% reduction of VLN™ compared to Top 3		**98%**	**98%**	**98%**	**97%**

Table VII.G-6. Comparison of VLN™ to Top 3 King Size Brands.

Product	**Market Position**	**Nicotine (mg/g tobacco filler)**	**Nicotine (mg/g tobacco filler; Dry Weight Basis)**	**Nicotine (mg/cigarette)**	**Nicotine (mg/cigarette (Smokie yield)**
Marlboro Gold King	1	15.9	18.2	10.3	0.67
Marlboro Red King	2	15.8	17.4	11.0	0.956

Newport Menthol Green King	3	17.9	20.3	12.0	1.08
Average Top 3		**16.5**	**18.6**	**11.1**	**0.902**
VLN™ King		0.41	0.47	0.27	0.03
VLN™ Menthol King		0.41	0.47	0.27	0.03
Average VLN™		**0.41**	**0.47**	**0.27**	**0.03**
% reduction of VLN™ compared to Top 3		**98%**	**98%**	**98%**	**97%**

3. "Helps you reduce your nicotine consumption" and "...greatly reduces your nicotine consumption."

VLN™ cigarette tobacco **contains** at least 95% less nicotine than the tobacco in conventional cigarettes. Under ISO conditions VLN™ yields 0.025 mg of nicotine per cigarette. The average yield for the top 100 brands in the U.S. is 0.93 mg/cigarette[18]. Under these test conditions VLN™ **yields** 97% less nicotine than conventional brands. That is, the tobacco content of VLN™ is reduced and the yield is also proportionately reduced. Upon smoking plasma levels of nicotine are proportionally reduced. Figure VII.G-1. Plasma nicotine levels after un-controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).., *Plasma nicotine levels after un-controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum)*, shows the plasma nicotine profile after smoking a single VLN™ cigarette in an uncontrolled manner (i.e. not structured smoking)[19]. Figure VII.G-2. Baseline adjusted plasma nicotine levels after controlled use (Log Scale) (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).,

[18] These results are from the filler nicotine analysis of the top 100 brands. See Section VIII.A.1.2. Filler Nicotine Content of Top 100 Brands.

[19] These results are from the abuse liability study. See Section VIII.C. Clinical Studies.

shows the PK data adjusted for baseline values on a log scale so it is possible to see the response to VLN™. Table VII.G-7 is a summary of the baseline-adjusted PK values. The plasma level after using the usual brand produced a quick rise peaking at 16.97 ng/ml at 7.85 minutes followed by a long decay. The gum results showed a slow rise peaking at 3.2 ng/ml at 28.7 minutes with a slow decay. VLN™ peaked at 0.57 ng/ml at 9.38 minutes with a slow decline demonstrating a response profile similar to conventional cigarettes. The VLN™ plasma nicotine levels were markedly less than usual brand and even less than nicotine gum. The plasma nicotine area under the curve (AUC) for VLN™ under controlled use conditions was 26.2 ng*min/ml. Usual brand was 770.8 and gum was 342.77. These results were statistically significant. The amount of nicotine absorbed (AUC) was 97% less than usual brand. The nicotine gum contained 4 mg of nicotine and VLN™ had 0.27 mg of nicotine/cigarette. On a content basis, VLN™ contained 92% less nicotine than the gum. The AUC for gum under controlled use was 342.77 and for VLN™ 26.2, a 93% reduction. Thus VLN™ cigarettes contain at least 95% less nicotine in the tobacco, yield at least 97% less nicotine in the smoke, and result in about 97% less nicotine in the plasma after smoking.

It has been suggested that smokers might compensate for the lower nicotine levels by smoking more cigarettes or altering how they smoke. As demonstrated above, smokers actually reduce their cigarette consumption over time. To get an equivalent amount of nicotine, smokers would need to smoke at least 20 more VLN™ cigarettes to get the same amount of nicotine as they were getting from one of their usual brands. For a pack a day smoker this would be

equivalent to two cartons per day or 400 cigarettes. This probably represents a physical impossibility. The maximum number of cigarettes smoked per day is reported as 90[20].

Compensation is often measured by CO boost. VLN™ cigarettes produce about the same level of CO as conventional cigarettes. Conceptually if smokers increased how much they smoked, their exhaled CO would increase (CO boost). Exhaled CO has been measured in many studies and there have been no measured increases (Table VII. G-8). Figure VII.G-3*., Exhaled Carbon Monoxide After 20-weeks*, shows the exhaled CO over 20-weeks of use of SPECTRUM (VLN™) cigarettes. CO levels are decreased because of the decreased cigarette consumption. Another measure of nicotine exposure is the total nicotine equivalents (TNE) in the urine. TNE is consistently reduced Nin studies with VLNC cigarettes (Table VII. G-8). Figure VII.G-4., *Total Nicotine Equivalents (TNE) After 20-weeks*, shows TNE after 20-weeks of use of SPECTRUM (VLN™) cigarettes. Urinary cotinine (a metabolite of nicotine) is a direct measure of nicotine exposure. In most studies continue is reduced to the same degree as nicotine or TNE (Table VII. G-8).[21]. **These studies demonstrate that use of VLN™ will result in a reduction in nicotine consumption validating the claim "Helps you reduce your nicotine consumption." The "… greatly reduces your nicotine consumption" claim is also supported by the data indicating that nicotine consumption is reduced.**

[20] The 2013-2014 NHANES dataset provides two measures of smoking frequency: cigarettes smoked per day at the time of quitting; and, the average number of cigarettes smoked per day in the last 30 days (CDC 2015). The minimum, calculated mean, and maximum number of cigarettes smoked per day at the time of quitting is 1, 14.7, and 95, respectively. The minimum, calculated mean, and maximum reported average number of cigarettes smoked per day during the last 30 days is 1, 8.4, and 90 cigarettes per day, respectively.

[21] In one study by Walker ((Walker *et al*. 2014), subjects were switched to Magic cigarettes (1.45 mg nicotine/g (wet weight); manufactured by 22nd Century) but were allowed to purchase and use their usual brand of cigarettes. Cotinine was reduced at 6 weeks but not at 12.

In almost all of the clinical studies, non-compliance (smoking non-study cigarettes) was detected. Even in cases where usual brand cigarettes were smoked in conjunction with VLNC cigarettes, biomarkers of exposure went down. Under normal use conditions, consumers will make decisions about how and when they choose to use VLN™ cigarettes. The benefit the smoker gets will be directly related to how compliant they are with their individual smoking plan. The statement does not mean that the product will **cause you** to reduce your nicotine consumption, it means that using the product will **help you** reduce your nicotine consumption when you are motivated to reduce it.

The statement "Helps reduce your nicotine consumption" is an explicit reduced exposure representation that the product or its smoke contains a reduced level of a nicotine and presents reduced exposure to a nicotine in the tobacco smoke. However, the statement will not be used alone and will accompany the primary claim "95% Less Nicotine" which is also a reduced exposure statement. Helps reduce your nicotine consumption is not being used a principal free-standing claim but as a modifying claim to bring meaning for the consumer of the principal claim "95% Less Nicotine." The statement is truthful and not misleading and is supported by extensive research.

Figure VII.G-1. Plasma nicotine levels after un-controlled use (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

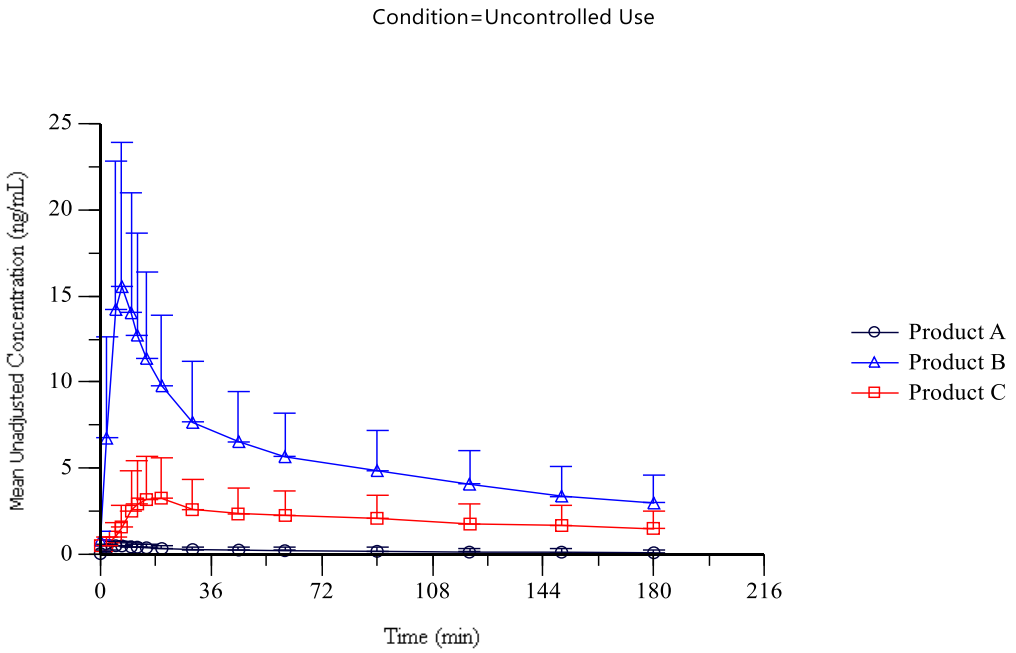


Figure VII.G-2. Baseline adjusted plasma nicotine levels after controlled use (Log Scale) (Product A = VLN™, Product B = Usual Brand, Product C = 4 mg Nicotine gum).

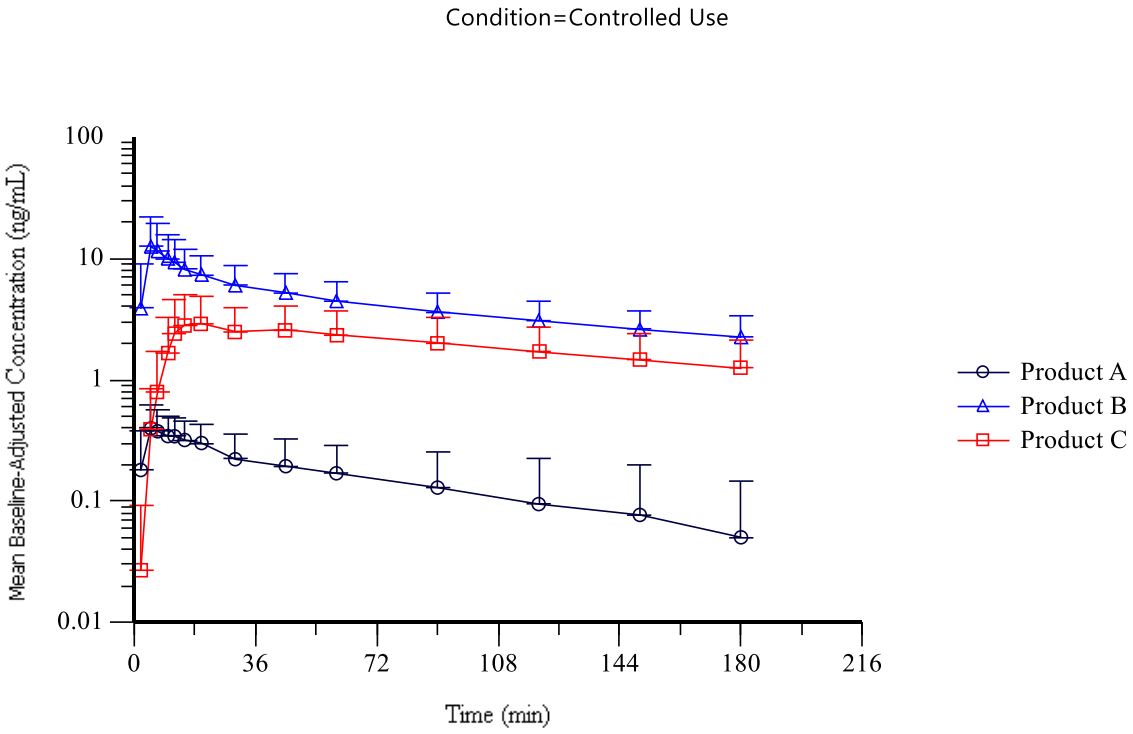


Table VII.G-7. Summary of baseline-adjusted plasma nicotine PK values. (From Altasciences 2018)

Product	Condition	AUC (ng*min/ml)	C_{max} (ng/ml)	t_{max} (min)	$T_{½}$ (min)	K_{el} (1/min)
Usual Brand	Controlled Use	770.80#	13.7#	8.29	123.49	0.0063
VLN™	Controlled Use	26.2*#	0.47*#	9.75	213.4	0.0098
Nicotine Gum	Controlled Use	342.77*	3.5*	33.6	125.36	0.0062
Usual Brand	Uncontrolled Use	879.75#	16.97#	7.85	101.89	0.0078
VLN™	Uncontrolled Use	28.3*#	0.57*#	9.38	110.8	0.0123
Nicotine Gum	Uncontrolled Use	277.3*	3.2*	28.7	166.42	0.0078

* p<0.05 to Usual Brand
# p<0.05 to Nicotine Gum

Table VII. G-8. Summary of biomarkers of exposure.

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Biomarker	Reference
VLN™	Single sessions	Evaluation of the abuse liability of very low nicotine cigarettes.	55	Decrease in plasma nicotine	Altasciences 2018 [pg89]
VLN™ Menthol	Single sessions	Evaluation of the abuse liability of	60	Decrease in plasma nicotine	Altasciences 2019

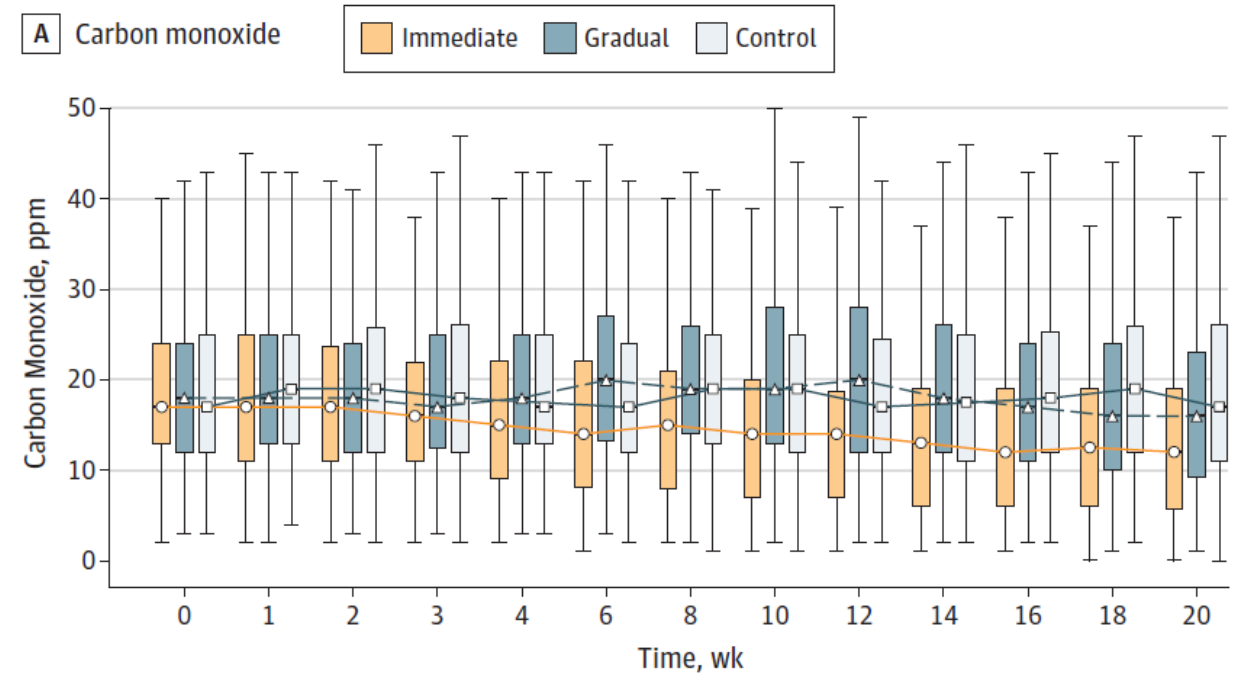
Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Biomarker	Reference
		menthol very low nicotine cigarettes.			[pg89]
Quest 3	6-weeks	Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation.	165	⇓91% Cotinine ⇓57% NNAL ⇓50% NNN ⇓50% 1-HOP NC 3-HPMA NC S-PMA NC CO	Hatsukami *et al*. 2010 [pg 94]
SPECTRUM	6-weeks	Randomized trial of reduced-nicotine standards for cigarettes.	840	⇓60% TNE ⇓61% Cotinine ⇓32% NNAL NC CO	Donny *et al*. 2015 [pg 92]
Quest 3	35-days	A randomized controlled trial of progressively reduced nicotine content cigarettes on smoking behaviors, biomarkers of exposure, and subjective ratings.	168	Progressive reduction nicotine over 35-days. ⇓66% Nicotine ⇓60% Cotinine* ⇓44% NNAL NC CO	Mercincavage *et al*. 2016 [pg 97]
SPECTRUM	5-days	Nicotine and anatabine exposure from very low nicotine content cigarettes.	23	⇓94% TNE ⇓92% Cotinine ⇓93 % Anatabine NC CO	Denlinger *et al*. 2016 [pg 91]
SPECTRUM	8-weeks	Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial.	136	⇓60% TNE ⇓47% NNAL NC CO With use of other combustible products	Hatsukami *et al*. 2017 [pg 94]
Magic	12-weeks	Abrupt nicotine reduction as an endgame policy: A randomized trial.	33	40% reduction in salivary Cotinine after 6 weeks; NC after 12 weeks. Subjects were free to use usual brand at the same time.	Walker *et al*. 2014 [pg 101])
SPECTRUM	6-weeks	Evaluation of a reduced nicotine product standard: Moderating effects of and impact on cannabis use.	717	BOE effects are combined for all SPECTRUM cigarettes (0.4 to 5.2 mg nicotine/g) NC in CO	Pacek *et al*. 2016 [pg 98]

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Biomarker	Reference
				TNE decreased.	
Quest 3 and Xodus	6-weeks	Reduced nicotine content cigarettes and nicotine patch.	219	⇓87% TNE ⇓88% Cotinine ⇓66% NNAL ⇓14% CO	Hatsukami *et al*. 2013 [pg94]
Quest 3	7-days	Reduced nicotine cigarettes: Smoking behavior and biomarkers of exposure in smokers not intending to quit.	72	⇓56% Cotinine ⇓17% 1-HOP ⇓28% CO	Hammond and O'Connor 2014 [pg 94]
Ultratech <0.06 mg Nicotine)	Single session	Pharmacodynamic effects of new de-nicotinized cigarettes.	20	Plasma levels of nicotine reduced. NC CO	Pickworth *et al*. 1999 [pg 98]
Quest and Xodus	6-weeks	Sex differences in response to reduced nicotine content cigarettes.	235	NC in CO ♂ ⇓20% CO ♀ NC TNE NC Cotinine NC NNAL	Vogel *et al*. 2014 [pg 101]
Quest 3	7-days	Mouth-level intake of benzo[a]pyrene from reduced nicotine cigarettes.	72	⇓ 70% Cotinine ⇓ 69% BaP NC 1-HOP	Ding *et al*. 2014 [pg92]
SPECTRUM	Single sessions and 1-week	Dose-response effects of spectrum research cigarettes.	51	⇓ 77% Cotinine ⇓ 75% TNE ⇓ 34% CO 7 Days	Hatsukami *et al*. 2013 [pg 94]
Ultratech (0.07 mg Nicotine)	Single session	Experimental evidence for a causal relationship between smoking lapse and relapse.	87	No CO boost	Juliano *et al*. 2006 [pg 95]
Ultratech	Single sessions	Placebo cigarettes in a spaced smoking paradigm.	8	No CO Boost	Eid *et al*. 2005 [pg 92]
Quest	Single sessions	Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls.	56	No CO Boost	Tidey *et al*. 2013 [pg 100]
SPECTRUM	Single sessions	Adolescent smokers' response to reducing	50	No CO Boost	Cassidy *et al*. 2018, *Drug*

Product	Cigarette Exposure Duration	Study/ Article Title	No. of Subjects	Biomarker	Reference
		the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations.			*and Alcohol Dependence* [pg 91]
Quest	Single sessions	Effects of low nicotine content cigarettes on smoke intake.	16	⇓ 26% CO ⇓ 86% Plasma Nicotine level after 8 hrs. of smoking compared to Now Ultra Light	Rose and Behm 2004 [pg 99]
SPECTRUM	6-weeks	Cigarette nicotine content as a moderator of the relationship between negative effect and smoking.	717	⇓ 39% Cotinine	Robinson *et al*. 2017 [pg 99]
SPECTRUM	6-weeks	Estimation of compliance with exclusive smoking of very low nicotine content cigarettes using plasma cotinine.	100	⇓ 61% Cotinine ⇓ 21% CO	Foulds *et al*. 2018 [pg 93]
SPECTRUM	20-weeks	Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial.	1250	⇓ 18% CO ⇓ 59% TNE ⇓ 35% NNAL ⇓ 21% 3-HPMA ⇓ 14% PheT ⇓ 31% CEMA ⇓ 25% HMPMA ⇓ 23% SPMA ⇓ 17% 2-HPMA	Hatsukami *et al*. 2018 [pg 94]

*Values not reported in original publication. Values extracted from figures in the publication.

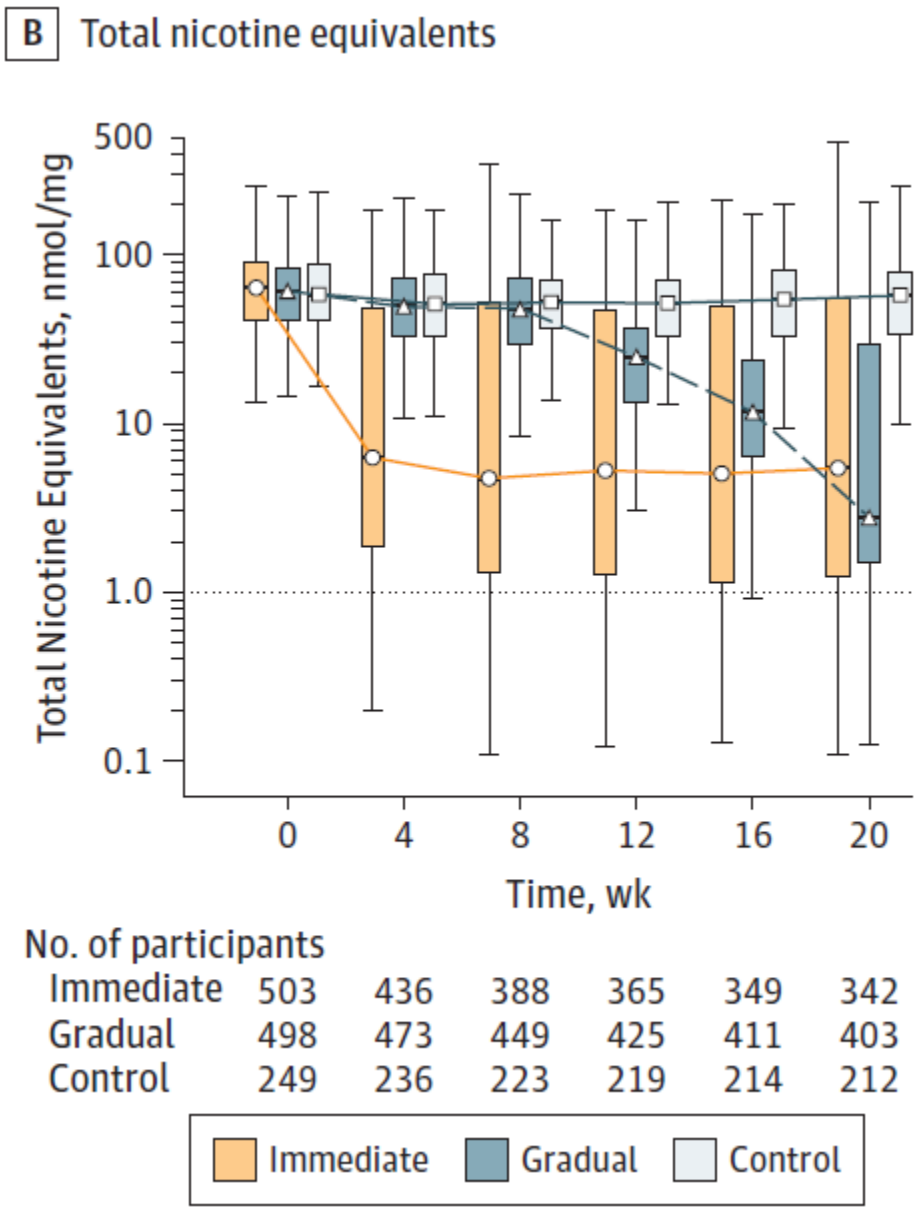
Figure VII.G-3. Exhaled Carbon Monoxide after 20-weeks (From Hatsukami *et al*. 2018 [pg 94]).



No. of participants

Immediate	503	459	428	405	416	394	380	357	359	341	348	335	342
Gradual	498	480	473	465	468	450	445	424	424	410	410	402	403
Control	249	240	233	227	234	221	222	212	218	213	214	210	213

Figure VII.G-4. Total nicotine equivalents (TNE) after 20-weeks (From Hatsukami *et al*. 2018 [pg 94]).



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