9.1.11.2.Drug Liking (Primary Outcome Variable). Review's Analysis (Data Tables and Computer Programs in Appendix 1 and 2, Respectively)

The first of the sponsor's primary outcome variables was drug liking. This was measured on a 100mm VAS in response to the question "Do you like the drug effect?" The extremes of the scale were labeled "Not at all" and "Extremely." A summary of maximal individual subject responses to this question for the primary treatment conditions are summarized in the table below. For this analysis, responses of less than 25 were considered negative (did not like the drug), while higher scores were considered a positive response.

A single maximum response was used in this analysis for 2 reasons: 1) Using the maximum response to a given treatment is more likely to show its greatest abuse liability and it is felt that the abuse of any drug is more likely to be function of maximum obtainable response and the predictability of that response; 2) Collapsing values to the single maximum response across time within a treatment condition was felt to be the best way to assure that the maximum pharmacological response to each treatment was captured. While the sponsor's approach of arranging the study dosing schedule such that pharmacological peak effects are expected to coincide across treatments is an acceptable way of approaching this issue, there is no way to assess the extent to which the sponsor may have been successful in this instance. Analyzing the maximum response regardless of time of occurrence was therefore the best available approach to this data.

Collapsing across doses for active Nicorette treatments by flavor is perhaps more statistically suspect in the sense that such an analysis will introduce a bias by potentially giving Nicorette more "chances" to appear positive relative to other treatments. This was considered an acceptable approach for the following reasons: 1) Visual inspection of the data (See Appendix 1) suggests that for some subjects increasing the dose to 8mg decreased the maximum response). It was felt to be unreasonable to assert that if someone were going to abuse Nicorette he would *necessarily* chose the highest dose *rather* than the dose that produced his maximal response. 2) The comparison between the different flavors of Nicorette is not expected to be effected by collapsing across doses since both products were tested an equal number of times. 3) A 20mg dose is expected to produce a robust response. If the maximum response to Nicorette were to exceed that of 20mg amphetamine, this would clearly be cause for concern.

Another analysis, a rank order analysis of the data, is also shown below. This analysis complements the analysis above in that it compares the relative preference of each subject for each treatment. Average of the relative rankings by treatment allow measurement of subject preference that is relatively free of the effects of the high variability seen in the sponsor's analysis.

Statistical analysis was not attempted since the sample size was small and the analysis is clearly exploratory/explanatory in nature.

Table 7 Number of Subjects Responding Positively to Each Treatment

SUBJ #	SMOKING	ACTIV ORIG GUM	ORIG FLAVOR GUM PLACEB O
Old	3	7	
Young	0	5	3
All	3	12	

Responses to the question "Do you like the drug effect?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. For the purpose of this analysis, subjects with VAS scores of >=25 were considered positive. Individual numeric responses and the corresponding codings, including responses to different doses of nicotine and confectionery mint and fruit flavor gum are shown in the appendix.

Table 8 Summary of Maximum Individual Responses to the Question "Do You Like the Drug Effect?" by Treatment Condition By Rank Ordering

	Cig	Placebo
Average	6.6	
Min		
Max		
Median		
Mode	7	

Responses to the question "Do you like the drug effect?" were recorded on a 100mm VAS for each treatment condition. These results were ranked by the reviewer as follows: Products were rated in rank order within subject. The treatment with the highest VAS response was given a score of 1, the lowest response was given a score of 9. Ties were assigned the average value. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score used in the ranking.

Inspection of this data reveals several problems with the sponsor's analysis and conclusions from this study:

First, this question does not appear to have been asked in a way that was capable of reliably discerning the drug effects of nicotine. Most of these subjects would appear not to have liked cigarettes particularly, with only 3 giving positive responses. While there may be a methodological reason for this (namely that in an outpatient study there was not good control of subjects smoking between sessions which may have affected their responsiveness to smoking), it is difficult to understand why such an effect would not also occur in subject's responses to Nicorette.

Second with respect to the question of interest, namely the abuse liability of Mint Nicorette, this analysis shows evidence of a somewhat higher drug effect for Mint compared to Original Nicorette. For both product flavors, active Nicorette is ranked higher than placebo in both analyses, suggesting that the study is indeed detecting the effects of nicotine in Nicorette,

however modest these effects may be. Ten subjects of 24 responded positively to the active mint. When these same 24 subjects were tested with Original Nicorette, 12 of them responded positively. Although the number of subjects who responded positively to Mint Nicorette in the categorical analysis may be less than the number responding positively to the Original flavor, the ranking analysis suggests that Mint is more strongly liked than the original flavor product.

9.1.11.3.Other Outcome Measures (Reviewer's Analysis) (Data Tables and Computer Programs in Appendix 1 and 2, Respectively)

One of the outcome measures included in this study was an 11 item gum scale. Items such as taste, ease of chewing and sweetness were rated on 100mm VAS, the ends of which were labeled 'Not at all' and 'Extremely' The maximum responses of each subject in each treatment condition to Question 6 (Would you chew this gum just to get the drug effect?), Question 8 (How sweet is the gum?) and Question 10 (How much do you like the gum overall (taste plus drug effect)?) were summarized by the reviewer and are presented below.

9.1.11.3.1.Would You Chew This Gum Just to Get the Drug Effect?

This question was of interest to the reviewer because of all of the questions in the study, it seemed to most closely capture the essence of the agency's concern, namely would people abuse this drug? The number of subjects responding positively to each treatment and their relative rankings are shown in the following tables:

Table 9 Number of Subjects Responding Positively to the Question 'Would You Chew This Gum Just to Get the Drug Effect?'

SUBJ #	[redacted]	ACTIVE ORIG GUM	ORIG FLAVOR GUM PLACEBO	[redacted]
Old	[redacted]	7	4	[redacted]
Young	[redacted]	2	0	[redacted]
All	[redacted]	9	4	[redacted]

Responses to the question "Would you chew this gum just to get the drug effect?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. For the purpose of this analysis, subjects with VAS scores of >=25 were considered positive. Individual numeric responses and the corresponding codings, including responses to different doses of nicotine and confectionery mint and fruit flavor gum are shown in the appendix.

Table 10 Summary of Maximum Individual Responses to the Question 'Would You Chew This Gum Just to Get the Drug Effect?' By Rank Ordering

	Active Orig	Orig Placebo	
Average	4.1	5.7	.1
Min			
Max			
Median	4.5	8	4.5
Mode	6	8	7

Responses to the question "Would you chew this gum just to get the drug effect?" were recorded on a 100mm VAS for each treatment condition. These results were ranked by the reviewer as follows: Products were rated in rank order within subject. The treatment with the highest VAS response was given a score of 1, the lowest response was given a score of 8. Ties were assigned the average value. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score used in the ranking.

This data suggests that subjects are about equally likely to "chew the gum just to get the drug effect" regardless of the active drug since about half of the subjects (but not necessarily the same subjects) responded positively to both flavors of Nicorette and both flavors of amphetamine. Once again, there also seems to be a difference between active and placebo response to Nicorette, suggesting that Nicorette may indeed have positive subjective effects. The rankings once again suggest a slight preference for Mint Nicorette over Original Nicorette, but in this case there may also be a slight preference for Active Mint Nicorette over amphetamine.

9.1.11.3.2.How Sweet is the Gum?

While sweetness itself is not ordinarily considered a predictor of abuse liability, this question was of interest because any difference in palatability may result in more widespread use. A significantly increased use may be associated with an increase in the total amount of abuse of the product even if the product itself is not clearly distinguished from a similar product on classical measures of abuse.

Table 11 Number of Subjects Responding Positively to the Question 'How Sweet is The Gum?'

SUBJ #	ACTIVE ORIG GUM	ORIG FLAVOR GUM (PLACEBO)	
Old	2	5	
Young	3	3	
All	5	8	

Responses to the question "How sweet is the gum?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as

A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. For the purpose of this analysis, subjects with VAS scores of >=25 were considered positive. Individual numeric responses and the corresponding codings, including responses to different doses of nicotine and confectionery mint and fruit flavor gum are shown in the appendix.

Table 12 Summary of Maximum Individual Responses to the Question 'How Sweet is The Gum?' By Rank Ordering

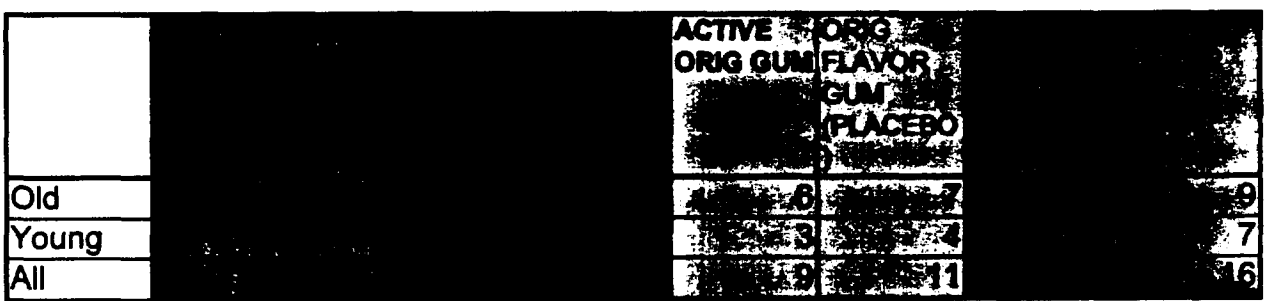
Responses to the question "How Sweet is the gum?" were recorded on a 100mm VAS for each treatment condition. These results were ranked by the reviewer as follows: Products were rated in rank order within subject. The treatment with the highest VAS response was given a score of 1, the lowest response was given a score of 8. Ties were assigned the average value. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score used in the ranking.

This data suggests that there is a difference between Mint Nicorette and confectionery gums in terms of sweetness, with virtually all subjects responding positively to the sweetness of confectionery gums compared to 14 subjects for Mint Nicorette. However, there also appears to be a difference between Original Flavor and Mint Nicorette that suggests that the Mint product may be sweeter than the Original.

9.1.11.3.3.How Much Do You Like the Gum Overall?

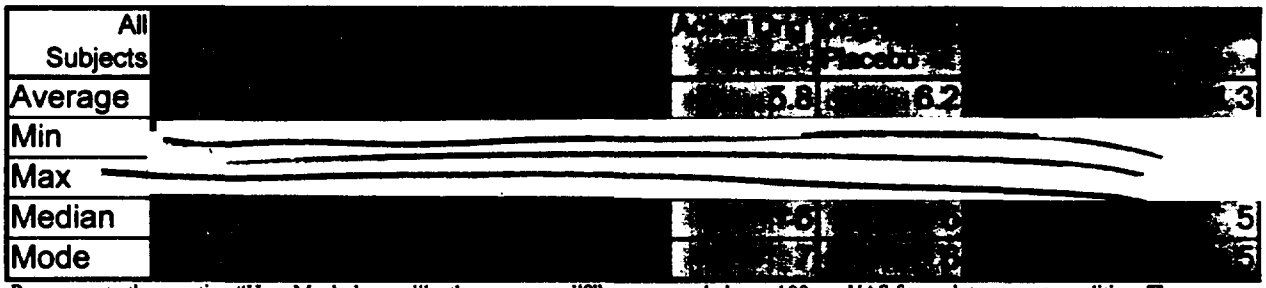
Finally, the same type of analysis was done on an overall measure of the qualities of the gum.

Table 13 Number of Subjects Responding Positively to the Question 'How Much Do You Like The Gum Overall?' By Rank Ordering



Responses to the question "How much do you like the gum overall?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. For the purpose of this analysis, subjects with VAS scores of >=25 were considered positive. Individual numeric responses and the corresponding codings, including responses to different doses of nicotine and confectionery mint and fruit flavor gum are shown in the appendix.

Table 14 Summary of Maximum Individual Responses to the Question 'How Much Do You Like The Gum Overall?' By Rank Ordering



Responses to the question "How Much do you like the gum overall?" were recorded on a 100mm VAS for each treatment condition. These results were ranked by the reviewer as follows: Products were rated in rank order within subject. The treatment with the highest VAS response was given a score of 1, the lowest response was given a score of 8. Ties were assigned the average value. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score used in the ranking.

The superiority of confectionery gum on this question suggests that for the most part subjects took this question to refer to qualities like flavor, sweetness and so forth. However, some of the response may have been motivated by the drug effects of the active gum, since as in response to drug liking, response to amphetamine seems less variable by flavor.

9.1.11.4.Effect Of Age On Response To Nicorette

At first glance, it may appear that younger subjects may be less likely to respond positively to Nicorette than older subjects. For example, 8 older subjects responded positively to Mint Nicorette vs. 2 of the younger subjects (Do you like the Drug Effect?). However, 10 older subjects responded positively to Mint Amphetamine for the same question while only 6 younger subjects did so. This suggests that the effect of age on the results of this study is a general effect that may more likely reflect the quality of younger people as subjects for abuse liability studies rather than reflect a lesser abuse liability of Nicorette by younger subjects.

9.1.11.5.Adverse Events

A total of 111 adverse events were reported in this study. A total of 55% were mild in severity, while 45% were rated as moderate. The sponsor reports no serious adverse events although one subject (#106) was seen in the hospital emergency room the evening after the 8mg Original Nicorette session where he was treated with Pedialyte for an apparent viral infection. Of the 37 subjects participating in this study 24 (65%) reported one or more adverse events. Adverse events were not untypical expected for a population of Nicorette or amphetamine users. A breakdown of adverse events is presented in the following table. Numbers of events (rather than percentages) are presented because amphetamine treatments are collapsed by gum flavor and not all 37 subjects completed the study. Not surprisingly, the majority of adverse events (including subject 23 discharged from the study for a moderate increase in blood pressure) occurred during

amphetamine administration. Of note, among the 37 subjects represented in this study (at least 24 of whom received at least 48 doses of amphetamine) there is only a single report of euphoria.

Table 15 Sponsor's COSTART Coding Of Total Number Of Subjects Experiencing Adverse Events Sorted In Order Of Decreasing Frequency By COSTART Term And Treatment Condition

	Total Events	Amph	Mint Pbo	Prac	8mg Mint	2mg Orig	4mg Orig	8mg Orig	Ong Pbo	Cig	4mg Mint	Gum	2mg Mint
Total Events	102	61	6	6	5	4	4	4	4	3	2	2	1
Insomnia	12	11							1				
Headache	10	3	2	1		1		1	1	1			
Hypertension	7	7											
Anorexia	5	4	1										
Asthenia	5			1	2				1		1		
Dyspepsia	5				1		1		1	1	1		
Nervousness	5	5											
Somnolence	5	1	2			1				1			
Tachycardia	5	5											
Emotion labil	4	3										1	
Unknown	4	3										1	
Hiccup	3				1		1						1
Nausea	3	2		1									
Tremor	3	3											
Pain	2					1	1						
Pain Chest	2	1						1					
Paresthesia	2		1	1									
Vomit	2	1		1									
Chills	1	1											
Conjunctivitis	1	1											
Diarrhea	1	1											
Dream Abn	1	1											
Euphoria	1	1											
Gingivitis	1							1					
Hallucin	1				1								
Hangover	1					1							
Hyperkinesia	1	1											
Hypertens	1			1									
Insomnia	1						1						
Migraine	1	1											
Mydriasis	1	1											
Nausea/Vom	1							1					
Neurosis	1	1											
Pain Pelvic	1	1											
Parosmia	1	1											

Sweat	1	1											

Transpose of table 12.2.1.1 from the sponsor's study report. Key to Treatment Conditions: Amph=Amphetamine;Mint Pbo=Mint Nicorette Placebo;Prac=Practice Session;8mg Mint=8mg Mint Nicorette;2mg Orig=2mg Orig Nicorette;4mg Orig=4mg Orig Nicorette;8mg Orig=8mg Orig Nicorette;Ong Pbo=Ong Nicorette Placebo;Cig=Cigarette Session;4mg Mint=4mg Mint Nicorette;Gum=Confectionary Gum;2mg Mint=2mg Mint Nicorette.

9.2. Marketing Study (S1330011)

9.2.1. Investigator(s) /Location

Morris Shelanski, MD
Product Investigations
151 East Tenth St
Conshohocken, PA 19428

and

Product Investigations, West
142 North Ninth Avenue, Suite 16
Modesto CA 95350

Start Date: 15 Dec 1997

Completion Date: 30 Jan 1998

9.2.2. Study Plan, Objectives & Rationale

This was a 2-center, outpatient, open-label, multiple-dose (1 dose of each flavor), randomized block 2-way crossover study. The study was intended to measure expectations and preference for Mint Nicorette compared with Original flavor Nicorette. Preference was measured for both light and heavy smokers and compared for smokers who had previously used Nicorette and those who had not.

9.2.3. Population

Major inclusion criteria were:

- Healthy male and female smokers aged 18 to 60
- Light Smokers (≤24 cigarettes per day) or Heavy Smokers (>24 cigarettes per day)
- Nicotine gum is one of the methods subjects would consider to help them quit.

Major exclusion criteria included:

- Clinically significant abnormal findings on the brief screening exam or medical history
- History of any clinically significant disease which in the opinion of the investigator would jeopardize the safety of the subject
- Inability to abstain from smoking during the treatment period
- Dentures or dental work that could affect the conduct of the study
- Any oral pathology
- History of allergic response or adverse reaction to nicotine gum, or patches
- Positive pregnancy test on study day

9.2.4. Design

Subjects were screened by phone and potentially eligible subjects were invited to the study site to complete a medical history and physical examination. Eligible subjects who agreed to participate were scheduled for a single return visit for the treatment phase of the study. The protocol called for the enrollment of 330 subjects who completed the study. These were stratified as follows:

Table 16 Protocol Specified Breakdown of Numbers of Subjects to be Recruited

	Light Smokers (<=24 cigarettes/day) Numbers of Subjects	Heavy Smokers (>24 cigarettes/day) Numbers of Subjects
Previously Used Nicorette	65	65
Never Used Nicorette	100	100

On the study day, subjects were asked respond to 2 concept boards (1 for each flavor of Nicorette to be tested). They were then given crackers and water followed by their first piece of Nicorette. Light smokers received 2mg Nicorette and Heavy smokers received 4mg Nicorette with flavors tested in random order across subjects. Gum was chewed as directed for 20 minutes and then subjects rated their first piece of gum. There was about 1 hour between the time subjects started chewing their first piece and the time they started chewing their second piece. Following crackers and water, the subjects chewed and rated the other flavor of gum in the same strength. Subjects then rated the taste of the second flavor and completed a final comparative rating of the 2 flavors.

9.2.5. Analysis Plan/Study Conduct

The study's null hypothesis was that there is no difference in the proportion of subjects preferring the Mint gum before and after tasting. It was assumed that Mint flavor would be preferred initially by 70% of subjects who had previously used Nicorette and by 60% of those who not and that 7.5% of those initially choosing Original flavor would subsequently choose

Mint flavor. Subjects were not to be replaced. Subjects who did not complete the crossover were to be dropped from the analysis.

The protocol was not amended after the start of the study.

A total of 18 subjects who completed the study were stratified incorrectly: 3 previous users were stratified into the never user group; 5 never users were stratified into the previous user group; 6 light smokers were stratified as heavy smokers; 3 heavy smokers were stratified as light smokers; and 1 subject was treated in the wrong order. Although the protocol made no mention of how errors in stratification were to be addressed, these subjects plus two additional subjects who failed to complete the study were excluded from the Evaluable population. All subjects who completed the protocol were included in the Intent To Treat population. The sponsor presents data from the Evaluable population in the study report itself. Data on the Intent To Treat population are included in the appendix to the report.

9.2.6. Patient Disposition

Table 17 Disposition of Enrolled Subjects

	Number of Subjects
Subjects Enrolled	343
Subjects Completing Study	341
Discontinued for Adverse Event: Nausea, Flushing, Shakiness, Burning in throat after 1st gum	1
Screening Failure: Would not buy Nicorette	1
Intent To Treat Population	341
Excluded From Evaluable Population	18
Evaluable Population	322

Tables 2 and 3 of the sponsor's study report.

9.2.7. Demographics/Group Comparability

Table 18 Demographics of 343 Randomized Subjects

	Light Smokers		Heavy Smokers	
	Never Used Nicorette (N=104)	Previously Used Nicorette (N=69)	Never Used Nicorette (N=102)	Previously Used Nicorette (N=68)
Age				
Mean±SD [range]	34.4 ±9.42 [18-60]	36.3 ±10.81 [18-58]	39.0 ±10.00 [18-59]	41.3 ±8.45 [19-59]
Gender				
Male	39 (37.5%)	17 (24.6%)	45 (44.1%)	32 (47.1%)
Female	65 (62.5%)	52 (75.4%)	57 (55.9%)	36 (52.9%)
Race				
Caucasian	86 (82.7%)	60 (87.0%)	87 (85.3%)	55 (80.9%)
Black	8 (7.7%)	2 (2.9%)	7 (6.9%)	6 (8.8%)
Asian	0 (0.0%)	1 (1.4%)	0(0.0%)	0 (0.0%)
Other	10 (9.6%)	6 (8.7%)	8 (7.8%)	7 (10.3%)

From table 4 of the sponsor's study report and table 1 of the Appendix to the study report

9.2.8. Results

9.2.8.1.Preference

As shown in the following table, subjects in this study initially showed a strong preference (more than 80%) for Mint flavor Nicorette. Some of this preference—particularly for lighter smokers—may have been tempered by the experience of using the gum, but the Mint flavor was still substantially preferred over the Original by all categories of smokers in the study.

Table 19 Overall Taste Preference for Mint and Original Nicorette

	Before Tasting Gum (%)		After Tasting Gum (%)	
	Mint	Original	Mint	Original
Light Smokers Previously Used NICORETTE	97	3	78	22
Light Smokers Never Used NICORETTE	88	12	82	18
Heavy Smokers Previously Used NICORETTE	84	16	80	20
Heavy Smokers Never Used NICORETTE	85	15	83	17

Table made by the reviewer from data in table 5.1 of the appendix to the sponsor's study report based on the Intent To Treat Population who answered both questions about flavor preference.

Initially, about 40% of subjects definitely or probably expressed an interest in buying Nicorette prior to trying the product, with the remainder saying they might buy the product or probably would not buy it. Only 1 subject (who appears to be the second subject dropped from the study) definitely would not buy the product—not an unexpected result since such persons were excluded at screening. After tasting the Mint flavor product, the proportion of subjects who definitely or probably would buy the product remained at about 40% and about 15% definitely would not buy it. After tasting the Original flavor, only about 20% of subjects would definitely buy the product and about 30% definitely would not buy it.

About 25% of subjects rated the Mint gum tasting good or better, about 65% rated it as not so good or fair, while about 10% rated it as poor. Less than 10% of subjects rated the Original flavor as good or better in taste while about 55% rated it as not so good or fair, and about 35% of subjects rated it as poor tasting.

The Mint flavor was consistently preferred over the Original variety by about 2 to 1 in characteristics such as "helps me control cravings," "helps me quit smoking," and "I could feel it working." The Mint flavor was preferred about 3 to 1 over the Original for "it is easy to chew."

This data is important in that it provides data from a much larger sample of subjects than the sponsor's abuse liability study. The sponsor believes that the study is reassuring insofar as a majority of subjects continued to rate the Mint gum unfavorably. This is certainly true. However, the fact remains that the extent to which Mint Nicorette *is* improved over the Original may make Mint Nicorette a product that some may find more "abusable."

9.2.8.2.Adverse Events

Adverse events are summarized in the following table taken from the sponsor's study report.

Table 20 Total Number of Adverse Events

	Light Smokers		Heavy Smokers	
Adverse Event (AE)	Never Used NICORETTE	Previously Used NICORETTE	Never Used NICORETTE	Previously Used NICORETTE
	(N=103)	(N=69)	(N=102)	(N=68)
All Aes	68	26	77	55
Number (%) of subjects with at least 1 AE	**44(43%)**	**20(29%)**	**41(40%)**	**35(51%)**
Body As A Whole	**6 (8.8%)**	**1(3.8%)**	**1 (1.3%)**	**1 (1.8%)**
Headache	5 (7.4%)	1(3.8%)	1(1.3%)	0 (0.0%)
Abdominal Pain	1(1.5%)	0 (0.0%)	0 (0.0%)	1(1.8%)
Digestive	**14 (20.6%)**	**6 (23.1%)**	**21(27.3%)**	**14 (25.5%)**
Dry Mouth	0 (0.0%)	1(3.8%)	0 (0.0%)	0 (0.0%)
Dyspepsia	8(11.8%)	3(11.5%)	10(13.0%)	5(9.1%)
Dysphagia	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eructation	1(1.5%)	0 (0.0%)	0 (0.0%)0	2 (3.6%)
Nausea	2 (2.9%)	2 (7.7	11(14.3%)	7 (12.7%)
Vomiting	1(1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous System	**36 (52.9%)**	**14 (53.8%)**	**34 (44.2%)**	**30 (54.5%)**
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
Hypesthesia	1(1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervousness	0 (0.0%)	0 (0.0%)	3 (3.9%)	0 (0.0%)
Paresthesia	35 (51.3%)	14 (53.8%)	28 (36.4%)	28 (50.9%)
Vasodilation	0 (0.0%)	0 (0.0%)	3 (3.9%)	0 (0.0%)
Respiratory	**4(5.9%)**	**3(11.5%)**	**7(9.1%)**	**4(7.3%)**
Bronchitis	0 (0.0%)	0 (0.0%)	1(1.3%)	0 (0.0%)
Cough (Increased)	2 (2.9%)	2 (7.7%)	0 (0.0%)	1 (1.8%)
Hiccup	2 (2.9%)	0 (0.0%)	6 (7.8%)	3 (5.5%)
Sinusitis	0 (0.0%)	1(3.9%)	0 (0.0%)	0 (0.0%)
Skin/Appendages	**0 (0.0%)**	**0 (0.0%)**	**3 (3.9%)**	**0 (0.0%)**
Application Site Reaction	0 (0.0%)	0 (0.0%)	3 (3.9%)	0 (0.0%)
Special Senses	**8 (11.8%)**	**2 (7.7%)**	**11(14.3%)**	**6 (10.9%)**
Lacrimation	1(1.5%)	0 (0.0%)	0 (0.0%)	0(0.0%)
Taste Perversion	7 (10.3%)	2 (7.7%)	11(14.3%)	6(10.9%)

Table 5 of the sponsor's study report. Results are Number of patients (%). Percentage is calculated based upon the total number of adverse events in the respective group. Review of selected adverse events in line listings shows that the figures in this table reflect the numbers of subjects experiencing each event at least once.

At least 1 adverse event was experienced by 140 of 342 subjects who used at least 1 piece of gum (41%). Most (90%) of events were mild or moderate in severity. One subject (a women

who was a heavy smoker who had never used gum before) withdrew following a single piece of gum. She experienced nausea, flushing, shakiness, and burning in her throat. No deaths or serious or unexpected adverse events were reported. There is some suggestion in this data that persons who have not previously used Nicorette may be more likely to report adverse experiences. The sponsor has not analyzed this data for the incidence of adverse events by flavor or treatment period. Given the design of the study (single dose with a short washout period) such an analysis is not likely to be fruitful

9.3. Swedish Institute for Tobacco Studies Report "Adolescent Use Of NRT-Products (Data From The 1997 Survey Of Drug Use Among 16 Year Old Boys And Girls In Sweden)."

Mint Nicorette is intended to be more palatable than the Original flavor. If this change were to significantly increase use of the product, it might also affect adolescent appeal and adolescent use of the product even though the product is not for sale to persons under 18 years old. U.S. Data on use of nicotine replacement by adolescents is not currently available. The sponsor provided data on the use of Nicorette by Swedish adolescents which can be used to assess the possible extent of adolescent use of Nicorette.

9.3.1. Description of the Survey

The Swedish Council for Information on Alcohol and Other Drugs (CAN) performs an annual survey in March of each year on drug use among students in the 9th grade. The survey is designed to be nationally representative of Swedish students who are age 16 in the year of the survey. The survey is conducted anonymously during a single class period. The 1997 survey whose report is included in this NDA was conducted collaboratively by CAN and the Institute for Tobacco Studies (ITS) and included a special section on the use of NRT products. The analysis of this data was performed by ITS.

9.3.2. Results of the Survey

The results presented below should be considered in light of the following: 1. At the time of this survey, the inhaler had been available for about 3 months. Other products had been available for several years. 2. At the same time that the inhaler was introduced in Sweden, an age limit was introduced forbidding sale of NRT products (as well as tobacco) to persons under 18. 3. The dropout rate (not filling out a survey) is about 15%. Prior surveys of dropouts have shown a somewhat higher rate of consumption in this category.

Respondents included 2908 boys and 2727 girls. Responses to all the questions presented in the report are shown on the following pages.

To: All Respondents
TOBACCO USE

	SMOKING			SNUFF			ANY TOBACCO		
	BOYS	GIRLS	TOTAL	BOYS	GIRLS	TOTAL	BOYS	GIRLS	TOTAL
DAILY	9%	12%	11%	11%	1%	6%	20%	16%	18%
ALMOST DAILY	3%	3%	3%						
LESS OFTEN	11%	14%	12%	7%	2%	5%	10%	14%	12%
QUIT/JUST TRIED	46%	39%	43%	37%	25%	31%	43%	40%	42%
NEVER AT ALL	32%	31%	31%	44%	72%	58%	27%	30%	28%
N	2871	2709	5580	2871	2705	5576	2853	2695	5548

Table 1 of the ITS Report.

The report notes that the distinction between use Less Often (then Daily or almost Daily use) and Quit or Just Tried is not very sharp while the distinction between Daily use, Almost Daily use and Never At All appears to be more sharply defined. While it may be true that the category Less Often (than Daily or Almost Daily) may be somewhat more open to interpretation than other categories, the most helpful distinction in this data is probably not between Daily/Almost Daily users and Never Users, but between those who have Never used/Quit/Just Tried tobacco other categories.

The report also notes that this data is unique insofar as the prevalence of daily smoking is higher among boys than girls. This difference was also 3% in 1997 and has varied between 2% and 8% over the last 10 years. The report also notes that the difference between boys and girls in daily smoking does not change with age. Thus, although there is some overlap between smoking and snuff use, the data do not suggest that use of snuff by Swedish youth is a precursor to cigarette use as it is in the United States.

To: All Respondents
WHICH ONE OR WHICH ONES NRT-PRODUCTS HAVE YOU USED?

	BOYS BY SMOKING STATUS						GIRLS BY SMOKING STATUS					
	DAILY	ALMOST DAILY	LESS OFTEN	QUIT/JUST TRIED	NEVER AT ALL	TOTAL	DAILY	ALMOST DAILY	LESS OFTEN	QUIT/JUST TRIED	NEVER AT ALL	TOTAL
GUM ONLY	24%	13%	12%	5%	1%	6%	25%	9%	5%	2%	1%	5%
PATCH ONLY	2%	0%	1%	0%	0%	0%	1%	0%	0%	0%	0%	0%
INHALER ONLY	4%	1%	1%	1%	0%	1%	7%	2%	1%	0%	0%	1%
GUM+ PATCH	5%	3%	2%	1%	0%	1%	7%	1%	1%	0%	0%	1%
GUM+ INHALER	9%	6%	2%	0%	0%	1%	8%	3%	1%	0%	0%	1%
PATCH+ INHALER	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
GUM+ PATCH+ INHALER	5%	1%	0%	0%	0%	1%	3%	1%	0%	0%	0%	0%
NO NRT PRODUCT	51%	75%	83%	93%	99%	90%	49%	83%	93%	97%	99%	91%
N	257	77	291	1261	890	2776	322	87	385	1033	825	2652

Table 2A of the ITS Report

Most (90%) of the students in this survey report not having used any nicotine replacement product at all. Among those who have used nicotine replacement, the gum is the most popular, used by about a quarter of daily smokers. The report notes that there is a relationship between the intensity of smoking and the use of nicotine replacement with use reported by half of daily smokers and by 1% of never smokers. While there does indeed appear to be such a relationship, about 13% of 16 year old boys and 5 to 9% of 16 year old girls who reported smoking less often than daily also reported using nicotine gum. In addition 5% of boys and 2% of girls who reported they had QUIT or JUST TRIED smoking had previously used nicotine gum. This is an area of concern since Nicorette has never been shown to be effective in persons under 18 nor has it been shown to be effective in persons who smoke less than daily. It certainly cannot offer a therapeutic benefit to 16 year olds who reported they JUST TRIED smoking.

To: Those who have used a NRT product
WHICH WAS THE LAST ONE THAT YOU USED?

	BOYS BY SMOKING STATUS						GIRLS BY SMOKING STATUS					
	DAILY	ALMOST DAILY	LESS OFTEN	QUIT/JUST TRIED	NEVER AT ALL	TOTAL	DAILY	ALMOST DAILY	LESS OFTEN	QUIT/JUST TRIED	NEVER AT ALL	TOTAL
GUM	66%	61%	84%	80%	85%	73%	60%	64%	75%	85%	75%	66%
PATCH	7%	11%	4%	11%	15%	8%	11%	7%	7%	11%	0%	10%
INHALER	28%	28%	12%	10%	0%	18%	29%	29%	18%	4%	25%	24%
N	120	18	49	83	13	283	164	14	28	27	8	241

Table 2B of the ITS Report

The gum retains its popularity among 16 year olds when asked which was the last NRT product they used. The report notes that at the time of this survey, the inhaler had only been available for about 3 months, whereas the gum and the patch had been available for several years. It is also reported that at the time of the introduction of the inhaler sales of NRT products to persons under age 18 were forbidden. If the figures in this table accurately reflect the number of respondents who reported using the inhaler in such a short period despite a ban on underage sales is remarkable.

TO: Those who have used a NRT-product
FOR HOW LONG DID YOU USE OR HAVE YOU BEEN USING THE PRODUCT?
(THE LAST ONE YOU HAVE USED OR ARE STILL USING NOW)

	BOYS BY LAST USED NRT PRODUCT				GIRLS BY LAST USED NRT PRODUCT			
	GUM	PATCH	INHALER	TOTAL	GUM	PATCH	INHALER	TOTAL
JUST AT A SINGLE OCCASION	72%	45%	75%	71%	68%	57%	68%	67%
A FEW DAYS	14%	27%	14%	15%	17%	13%	14%	16%
ABOUT 1 WEEK	6%	18%	6%	7%	7%	17%	8%	9%
ABOUT 2 WEEKS	3%	5%	4%	3%	5%	9%	5%	6%
ABOUT 1 MONTH	2%	5%	2%	2%	1%	0%	2%	1%
ABOUT 2-4 MONTHS	2%	0%	0%	1%	1%	0%	3%	1%
ABOUT 5-7 MONTHS	1%	0%	0%	0%	0%	0%	0%	0%
ABOUT 8-12 MONTHS	0%	0%	0%	0%	0%	0%	0%	0%
MORE THAN 1 YEAR	0%	0%	0%	0%	1%	4%	0%	1%
N	196	22	51	269	149	23	59	231

Table 3 of the ITS Report

It appears that most NRT use by survey respondents was on a single occasion or for brief periods. Even the patch which appears to have the longest duration of use is infrequently used for longer than 1 month. Once again, this data suggests an irregular pattern of use that has not been shown to be associated with a clinical benefit.

To: Those who have used a NRT-product more than just at a single Occasion
HOW OFTEN DID YOU USE/ABE YOU USING THE PRODUCT?

	BOYS BY LAST USED NRT PRODUCT				GIRLS BY LAST USED NRT PRODUCT			
	GUM	PATCH	INHALER	TOTAL	GUM	PATCH	INHALER	TOTAL
EACH DAY	33%	27%	62%	38%	50%	40%	68%	53%
EACH WEEK	19%	0%	8%	14%	10%	10%	0%	8%
LESS OFTEN	44%	45%	31%	42%	38%	40%	26%	35%
NO ANSWER	4%	27%	0%	6%	2%	10%	5%	4%.
N	54	11	13	78	48	10	19	77

Table 4 of the ITS report

Among those who used an NRT product on more than one occasion, less than half report daily use.

To: Those who have used a NRT-product more than just a single occasion
WHY DID YOU USE/ARE YOU USING THE PRODUCT? (CHECK ONE OR MORE BOXES)

	BOYS BY LAST USED NRT PRODUCT				GIRLS LAST USED NRT PRODUCT			
	GUM	PATCH	INHALER	TOTAL	GUM	PATCH	INHALER	TOTAL
STOP SMOKING	46%	36%	85%	51%	81%	50%	61%	72%
CUT DOWN SMOKING	15%	18%	38%	19%	33%	30%	28%	32%
STOP SNUFF USE	17%	18%	0%	14%	2%	10%	6%	4%
CUT DOWN SNUFF USE	9%	0%	0%	6%	0%	0%	0%	0%
EXPERIENCE THE DRUG EFFECTS OF NICOTINE	9%	9%	0%	8%	6%	0%	0%	4%
TRY BY CURIOSITY	9%	0%	8%	8%	4%	0%	11%	5%
OTHER	2%	0%	0%	1%	0%	0%	0%	0%
NO ANSWER	4%	27%	0%	6%	0%	20%	0%	3%
N	54	11	13	78	48	10	18	76

Table 5 of the ITS report

Among this same population of repeat users of NRT products, about half of the boys and 70% of the girls reported wanting to stop smoking as their reason for using the product. While such an intention indicates a potentially legitimate use of the product, about 5% of girls and 8% of boys reported Curiosity and Experiencing the Drug Effects of Nicotine as reasons for using these products, particularly the gum. The frequency of such responses suggest once again that adolescents may be motivated, at least in part, to use nicotine replacement products for inappropriate or improper reasons.

Although the numbers of respondents are too small to allow conclusions to be drawn, it is of interest that no one reported Experiencing the Drug Effects of Nicotine as a reason for using the inhaler and that no one tried the patch out of Curiosity.

To: Those who have used a NRT product more than just at a single Occasion
HOW DID YOU OBTAIN THE PRODUCT?

	BOYS BY LAST USED NRT PRODUCT				GIRLS BY LAST USED NRT PRODUCT			
	GUM	PATCH	INHALER	TOTAL	GUM	PATCH	INHALER	TOTAL
BOUGHT MYSELF	37%	18%	46%	36%	33%	0%	21%	26%
ASKED OTHERS TO BUY	15%	9%	31%	17%	17%	10%	21%	17%
WAS GIVEN	26%	45%	8%	26%	23%	30%	26%	25%
OTHER WAY	15%	0%	8%	12%	15%	50%	21%	21%
NO ANSWER	7%	27%	8%	10%	13%	10%	11%	12%
N	54	11	13	78	48	10	19	77

Table 6A of the ITS report

Among those who had used NRT regularly, about 1/3rd of the boys and 1/4th of the girls bought the products themselves. These numbers do not appear to be very different for the inhaler. The report notes that this "gives the impression that the age limit constituted some but not a very severe restraint."

To: Those who have used a NRT product just at a single occasion
HOW DID YOU OBTAIN THE PRODUCT?

	BOYS BY LAST USED NRT PRODUCT				GIRLS BY LAST USED NRT PRODUCT			
	GUM	PATCH	INHALER	TOTAL	GUM	PATCH	INHALER	TOTAL
BOUGHT MYSELF	12%	10%	13%	12%	7%	0%	20%	10%
ASKED OTHERS TO BUY	6%	10%	3%	5%	2%	8%	3%	3%
WAS GIVEN	62%	50%	76%	65%	68%	46%	65%	66%
OTHER WAY	13%	20%	5%	12%	19%	23%	8%	16%
NO ANSWER	6%	10%	3%	6%	4%	23%	5%	6%
N	141	10	38	189	101	13	40	154

Table 6B of the ITS report

Those who only used an NRT product once, appear to be less likely to have purchased the product themselves.

Additional analyses noted in the report noted the following:

Of the 2 users who reported using nicotine replacement for more than 1 year, both indicated that the reason for their use was to stop smoking. [It is not reported whether they may have given other reasons for use as well.]

Of the 6 "real users" of nicotine replacement who had never smoked at all (those who had used the product on more than a single occasion), none reported use longer than about 2 weeks. Two of these 6 were snuff users who indicated stopping or reducing snuff use as their reason for snuff use. One respondent indicated curiosity, 1 indicated a desire to experience the drug effects of nicotine and 2 did not answer the question about reasons for use.

9.3.3. Reviewer's Assessment

Of all of the nicotine replacement products covered in this survey, self titrated dosage forms Nicorette was the most popular among adolescents. There does seem to be a relationship between the frequency of reported smoking and the use of nicotine replacement, but some use was reported by those who smoked infrequently. There was some use of Nicorette for reasons of curiosity or to experience the drug effect of nicotine. The pattern of use was irregular, often being limited to a single occasion. This pattern of use does not suggest that adolescents are likely to derive therapeutic benefit from the use of Nicorette, and that restricting adolescent access to Nicorette is generally appropriate.

It is also important to note that teenagers obtained the product in a variety of ways including being given, purchasing for themselves, and asking other people to buy the product. The report notes that this data "gives the impression that the age limit [on purchase] constituted some but not a very severe restraint.[on adolescent access to Nicorette]" It is not known, however, whether the kids who reported buying the product for themselves appeared to be older than those who did not purchase the product for themselves. Nor is the extent of retailer compliance with the age restriction reported. The data suggest that an effective prohibition on the sale of Nicorette to minors is likely to be an important component of efforts to prevent adolescent misuse and abuse of Nicorette. Unfortunately, data on adolescent access to and use of Nicorette is not currently available for the U.S.

9.4. Qualitative Youth Appeal Assessment Reports

9.4.1. Description Of The Assessment

In response to the agency's concern about possible use of Nicorette by adolescents as a gateway product to nicotine dependence, the sponsor commissioned Teen Research Unlimited to conduct 13 adolescent focus groups to determine the youth appeal of this product. The first 3 sessions focused on Nicorette and NicoDerm. The next sessions focused on Mint Nicorette. Transcripts and video tapes of the 10 sessions conducted to assess the youth appeal of Mint Nicorette are included in this NDA. The sponsor's report for each series of focus groups for Mint Nicorette is also included, along with a summary report. The following description of the focus group sessions is based on the summary report.

Individual sessions were restricted to either boys or girls. The first 3 sessions in April of 1995 (focused on Original Nicorette and NicoDerm) included 9th and 10th graders. There was one group each of boys and girls who were occasional to regular smokers and one group of weight conscious girls. The next 10 sessions focused on Mint Nicorette and were conducted between November 1996 and July of 1997. The first 4 of these sessions were conducted among 9th and 10th grade boys and girls, with separate sessions for smokers and nonsmokers. Then there were 2 sessions among 9th to 11th grade boys who were either heavy or occasional smokeless tobacco users. The final 4 sessions included 7th and 8th grade boys and girls who were believed to be

either at high risk or low risk for smoking. The total number of kids interviewed in these focus groups was about 75.

Sessions began with a discussion of teen social life that included discussions of drinking, drugs, cigarette and smokeless tobacco use. Following this 4 concept products were shown to the participants. Concepts were presented in random order across focus groups, and all concepts were presented similarly to mask the focus on Nicorette. Information presented about these products is shown in the following table:

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Table 21 Product Descriptions Used In Adolescent Focus Groups

Product	Description Provided
Blast! (Double Caffeine Cola)	**Heading:** "I like the refreshment of soda...but sometimes I need more of a boost." **Graphic:** Picture of a bottle with word Blast and a bolt of lightening on the label. **Below Graphic:** "Introducing BLAST! New Blast! is a soda and a half! It's got a refreshing delicious cola taste that will knock your socks off. And Blast! combines the quick energy of sugar with double the caffeine of ordinary sodas, to give you an invigorating blast of super high energy."
Pro Fuel (Replenishing vitamin for athletes)	**Heading:** "I work out really hard. So I need to really fuel up and replenish all of my strength" **Graphic:** Picture of a bottle with the word PROFUEL and a picture of a body builder on the label. **Below Graphic:** "Introducing PRO-FUEL! New PRO_FUEL is an extra strength amino acid supplement created for athletes to replenish, energize and fuel up on protein with meals and after a tough workout. PRO-FUEL! is a concentrated source of amino acids derived from whey protein, which experts consider to be the 'perfect' and most efficient protein source"
CHEROKEE Gold (Smokeless Tobacco) [Exposed to males only]	**Heading:** "I'm not a smoker, but I love that tobacco feeling. Introducing CHEROKEE GOLD" **Graphic:** Picture of a can labeled *Cherokee* GOLD SMOKELESS TOBACCO **Below Graphic:** "Cherokee Gold is the newest chewing tobacco on the scene. It gives you a rich mellow taste with just a hint of mint...and leaves you with an energizing hit of tobacco refreshment."
NoZs (a stay awake aid)	**Heading:** "Sometimes I need to stay awake...and coffee and soft drinks just don't do it." **Graphic:** Picture of a box that contains the word **NoZs**. Below Graphic: "Introducing NoZ's. NoZ's is a new non prescription created to keep you wide awake when you really need to be. NoZ's gives you an intense dose of caffeine in each tablet...much more stay awake power than you get from the usual coffee guzzling and chugging down sodas."
Mint Nicorette	**Heading:** "I really want to quit smoking...but it's so hard to fight the cravings. I just can't do it without help" **Graphic:** A box with the SB logo and *Mint Flavor* NICORETTE GUM. Next to the box are 4 blister-packed pieces of Nicorette. **Below Graphic:** "Introducing NICORETTE with Mint Flavor. Nicorette nicotine gum is now available with mint flavoring. Nicorette nicotine gum can increase your chance of success in quitting smoking. Nicorette gum helps you control how much nicotine you use and when you use it."

Concept Products were presented in random order pill was presented to groups of girls only. Its description is not provided.

After the concepts were presented on illustration boards, copies of the concepts were passed out and participants were asked to sort the products into 2 piles: those in which they were personally interested and those in which they were not. They were asked to rank order all products. Respondents then discussed their reasons for their rankings and described who they thought would be most interested in each product.

Discussion then focused on Nicorette. Anticipated price was discussed. After discussion, placebo Nicorette was sampled. Then the teenagers were told of the manufacturers concern about Nicorette and directly questioned about this issue. [Although not described in the summary report, another nicotine product—apparently the nicotine inhaler—was also introduced to the respondents at the end of some of the sessions.]

9.4.2. Sponsor's Assessment

The sponsor believes that the data from these focus groups consistently supports the following conclusions:

1. Teens do not find either flavor of Nicorette appealing and widespread abuse of the product is not expected.

2. The only respondents who were interested in Nicorette were regular smokers who were said they were seriously committed to ending their cigarette smoking behavior. These teens would probably only use Nicorette if they were emotionally and financially supported by their parents.

3. The psychological motivations for teenage tobacco initiation—belonging, acceptance, affiliation, and experimentation—would clearly *not* be satisfied by a nicotine gum no matter what the flavor or taste.

9.4.3. Reviewer's Assessment

The reviewer is concerned that the sponsor's description of the results of these studies might be overly reassuring for the following reasons:

1. Some of the quotes in the sponsor's summaries are far from exculpatory. Examples that suggest possibly greater teen interest in the Nicorette (if presented appropriately) include the following:

- "It might taste better than tobacco, be easier to hide in school—but who could afford it?" This quote from a smokeless tobacco user gives Nicorette a disadvantage only in price.

- "Even though one respondent thought some teens might consider sneaking or stealing Nicorette gum, neither he nor his fellow respondents said they personally would ever consider buying or stealing it." While this statement may not seem particularly surprising,

the acknowledgement by kids that some kids might consider buying or stealing the product is hardly exculpatory.

2. Nicorette was clearly presented as a medicine, while the other products were presented in terms that clearly suggested the possibility of use intended to cause significant positive effects (e.g., an 'invigorating blast of super high energy' from caffeine and sugar for Blast!, an 'intense dose of caffeine' for noses, 'an energizing hit of tobacco refreshment' for Cherokee Gold, etc). This difference in presentation is clearly reflected in relative ratings of Nicorette and the other products. Unfortunately, the fact that there are 2 strengths of Nicorette, the higher strength of which delivers an amount of nicotine not terribly different from a cigarette does not appear to have been discussed. Nor was the possibility presented that Nicorette may be used in a way that may produce effects similar to those seen from smoking or using smokeless tobacco. There is therefore no reason to believe that if Nicorette were presented to teenagers the way that cigarettes or smokeless tobacco are, that they might not be interested in using it (e.g. as a way to get nicotine surreptitiously at school). Indeed, in the SIFO survey, 9% of respondents reported using Nicorette on more than a single occasion listed curiosity or to experiencing the effects of Nicotine among their reasons for doing so.

   To be sure, responsible marketing of Nicorette as was presented in the focus groups is an essential element in controlling adolescent use of this product. However, it should not be assumed that such a presentation to teenagers is the only presentation that teenagers will receive. Therefore, the case against adolescent misuse or abuse of Nicorette made by the focus group data is not at all clear cut.

3. A substantial emphasis was placed by the sponsor on the price sensitivity of teens to Nicorette. While this may be true, it is important to remember that a great many teens do not buy their cigarettes preferring to get them from others (or possibly from theft). One can hardly expect that the price of a product will substantially impact its use if the users do not pay for the product. The SIFO survey points out that this behavior (obtaining the product through means other than purchase) is also to be expected for Nicorette. Another problem with relying on price sensitivity as a means to discourage teens from using Nicorette, is that the price of Nicorette quoted in the focus groups ($28 for 48 pieces, $54 for 108 pieces) does not consider the inevitable decrease in the relative price of Nicorette—from both generic competition and from an increases in the price of cigarettes through taxation.

4. The sponsor emphasizes the poor taste of Nicorette as another factor discouraging teens from misusing the product. Yet tobacco products are widely abused by teenagers despite the generally poor sensory appeal of the products.

5. The standard applied by the sponsor for the determination of abusability appears to have been too high. For example, the interviews emphasized kids negative responses to the question of whether Nicorette would become the "Next Big Teen Thing." A negative response to such a question is hardly reassuring. Indeed, in the focus group of boys at high

risk for smoking (N=5), all respondents seem to have responded negatively to the question of whether Nicorette would become the next "Big Teen Thing." Yet, 2 participants expressed an interest in trying Nicorette, but seem to have been dissuaded from this opinion by questioning from the moderator that seemed to be different from questioning about other products. Later in the same session, during discussions of price, one of the boys reported that his friends stole Nicorette from Walgreen's, where it was easier to get Nicorette than cigarettes. Cigarettes were kept behind the counter. Nicorette was kept out with the smokeless tobacco. The phrase "Cigarette Gum" was used by one of the participants to describe Nicorette. When offered Nicorette to try, only one of the boys seems to have initially turned it down, and all of them seem to have taken a sample. (They were not told till later that it was placebo.)

The focus group data highlight the importance of product promotion and presentation on adolescent appeal. They do not, however, demonstrate that Nicorette's medicinal image is so strong that it will not appeal to a significant number of adolescents. Although Nicorette may be perceived as an adult medication by many teenagers, the overall tenor of this data suggests that teenagers will try Nicorette if offered an opportunity to do so by someone they trust.

9.5. Deaths

No deaths occurred among subjects in the studies in this NDA.

9.6. Other Safety Findings

9.6.1. ADR Incidence Tables

See individual study reviews.

10. Labeling Review

Labeling to be reviewed by DODP. There are no labeling issues with respect to abuse liability that need to be brought to the attention of DODP by the division.

11. Conclusions

11.1. Abuse Liability Study

Although the sponsor reports no difference in abuse liability between Mint and Original Nicorette, the actual situation is somewhat less clear. Individual responses to drugs are highly variable. Within this variability there do appear to be subjects who respond quite positively to the mint gum, such that the overall abuse liability of Mint Nicorette can fairly be said to be somewhat greater than the Original Nicorette. Unfortunately, the study also seems to show that the abuse liability of Nicorette is equal to 20 mg of amphetamine and more than a cigarette.

Because of these other findings, the clinical significance of the differences in abuse liability between Mint and Original Nicorette must come largely from outside this study.

While it is perhaps of concern to find that an OTC smoking cessation product has an abuse liability similar to a schedule II drug, this finding is not quite so surprising when one considers that subjects in this study were not amphetamine abusers, but they were dependent on nicotine. This would be expected to decrease the positive response to amphetamine while maintaining a relatively robust response to small amounts of nicotine. Unfortunately, subjects in this study did not respond particularly strongly, even to cigarettes.

11.2. Marketing Study

Most of the subjects in the marketing study initially preferred Mint to Original Nicorette. While this preference continued after tasting the product, the magnitude of the preference was attenuated by the experience. Indeed, most of the subjects in the marketing study found both the Original and Mint flavors of Nicorette unpalatable to varying degrees.

However, the data show enough differences between Mint and Original flavor to conclude that the change in flavor may well result in a more acceptable product. For example, subjects were more likely to be interested in buying Mint rather than Original Nicorette after tasting the products, and the taste of Mint Nicorette was rated more favorably than Original.

The differences between the products do not appear to be large enough to suggest that Mint Nicorette presents a significant abuse liability risk in a population of addicted adult smokers who want to quit.

11.3. Swedish Institute for Tobacco Studies (SIFO) Report

The SIFO report provides at least some data to suggest that Nicorette may be used for its drug effects or for curiosity, in addition to trying to quit smoking. Unfortunately, little data exist on the extent of adolescent use of Nicorette in the U.S. At the time of the approval of Nicorette for OTC sale in this country the sponsor committed to "conduct a surveillance study designed to identify and report on sale to or use by people less than 18 years of age." The sponsor attempted to fulfill this commitment by incorporating questions on nicotine replacement therapy on nationally syndicated surveys of drug use. They have been unable to obtain agreement to do so. The commitment remains to be fulfilled.

Unfortunately, the true extent of the potential problem of adolescent abuse of Nicorette remains unknown because the sponsor has failed to fulfill their phase IV commitment to

11.4. Qualitative Youth Appeal Assessments

While far from the usual scientific standard of the agency, the sponsor's focus groups suggest that the presentation of the product in the marketplace, price and taste can have a significant

impact on the abuse of the product by adolescents. In such a situation while cigarettes and chewing tobacco may be more appealing to many kids than Nicorette, the SIFO report provides at least some data to suggest that Nicorette may be used for its drug effects or for curiosity, in addition to trying to quit smoking.

11.5. Overall Conclusion

The available data suggest that Mint Nicorette may indeed provide a sufficiently more palatable alternative to the Original flavor to encourage more adults to attempt to quit smoking. The change in flavor does not appear to present a significant abuse liability risk to adult smokers who might use the product.

The impact of a change in flavor and possible wider use on adolescent access to the product is unknown. While the relative price of Nicorette compared to cigarettes may deter may youngsters from using the product as an alternative to cigarettes or smokeless tobacco, this may not always be the case. It is well to remember that sponsors emphasized to the agency that smoking cessation products would be priced comparably to cigarettes. Generic smoking cessation products will be available shortly. When this happens, the price of Nicorette will surely come down. At the same time, the price of cigarettes may rise with increases in taxes. If this happens, the agency will need to depend more and more on the effectiveness of the ban on the sale of Nicorette to minors, the sponsor's measures to minimize theft, and other aspects of marketing to deter abuse of the product by adolescents.

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12. Recommendations

Adequate information on the abuse liability of Mint Nicorette has been presented to allow the product to be approved.

The sponsor should be required to fulfill their phase 4 commitment to. "conduct a surveillance study designed to identify and report on sale to or use by people less than 18 years of age." This survey should be conducted on an ongoing basis and should be based on a sample of high school students large enough to be nationally projectable.

The sponsor should be required to monitor the effectiveness of the ban on sales to adolescents. It is recommended that the program include an adolescent "buying program," to identify retail establishments who are not complying with the age restriction on sales. This program should focus on "high risk" retailers (e.g. those retailers who have been cited by local tobacco buying programs, who not store Nicorette in locked cabinets, who stock Nicorette together with chewing tobacco, or who do not use theft surveillance tags to deter theft.)

/S/ 11/30/98

E Douglas Kramer, MD
Medical Officer

/S/ 11/30/98

Celia Winchell, MD
Medical Team Leader, Drug Abuse

/S/ 11/30/98

Michael Klein, Ph.D.
Team Leader, Controlled Substances.

CC:
IND 18612 Div File
HFD-170 Kramer/Klein/Permutt/Winchell/McCormick
HFD-170 Doddapaneni
HFD-170 Kumar
HFD-170 Klein

13. Appendix 1 Maximum Individual Responses to Questions in Study MD 01011

Table 22 Maximum Individual Responses to the Question "Do You Like the Drug Effect?" by Treatment Condition

Sub #						Mint Placebo	Cig				Orig Placebo		
1						0	0			0	8		
2						75	6			4	0		
3						1	0			48	57		
4						1	1			1	1		
7						52	53			48	46		
8						87	0			7	0		
9						2	0			90	1		
11						1	53			31	1		
12						69	45			34	62		
14						17	2			55	24		
15						5	0			0	41		
16						0	0			32	0		
18						6	0			0	90		
20						34	14			18	33		
22						0	0			0	0		
24						0	0			0	100		
106						100	0			49	0		
117						1	0			0	1		
119						1	0			0	0		
121						11	9			3	1		
123						0	0			0	1		
205						0	0			0	0		
210						0	0			82	15		
313						0	0			0	0		

Table made by the reviewer from the sponsor's SAS data set (DEFFALLT). Responses ranged from "Not at all"=0 to "Extremely"=100. **Subject numbers for younger subjects are shown in bold.**

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ON ORIGINAL

Table 23 Summary of Maximum Individual Responses to the Question "Do You Like the Drug Effect?" by Treatment Condition

SUBJ #	SMOKING	ACTIV... ORIG... GU...	[redacted]
1	NO	NO	NO
2	NO	NO	NO
3	NO	SOME	SOME
4	NO	NO	NO
7	SOME	SOME	SOME
8	NO	NO	NO
9	NO	A LOT	NO
11	SOME	SOME	NO
12	SOME	SOME	SOME
14	NO	A LOT	NO
15	NO	A LOT	SOME
16	NO	SOME	NO
18	NO	SOME	A LOT
20	NO	SOME	SOME
22	NO	NO	NO
24	NO	NO	A LOT
106	NO	SOME	NO
117	NO	NO	NO
119	NO	NO	NO
121	NO	NO	NO
123	NO	NO	NO
205	NO	NO	NO
210	NO	A LOT	NO
313	NO	NO	NO

Responses to the question "Do you like the drug effect?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. **Subject Numbers for Younger subjects are shown in bold.**

Table 24 Maximum Individual Responses To The Question "Would You Chew This Gum Just To Get The Drug Effect?"

SUB #	MINT PLACEBO	ORIG 4MG	ORIG 8MG	ORIG PLACEBO
1	3	0	0	0
2	55	4	4	15
3	1	1	1	52
4	0	1	1	0
7	47	48	48	46
8	89	80	76	0
9	1	82	87	1
11	40	45	24	1
12	75	55	27	46
14	6	38	64	27
15	2	0	0	0
16	0	0	0	0
18	13	5	1	0
20	21	50	21	8
22	0	0	0	0
24	0	0	0	0
106	100	0	0	0
117	2	0	0	0
119	1	0	0	0
121	0	0	0	0
123	0	0	7	1
205	0	0	0	0
210	0	0	56	18
313	0	0	0	0

Table made by the reviewer from the sponsor's SAS data set (GUMALLT). Responses ranged from "Not at all"=0 to "Extremely"=100. **Subject numbers for younger subjects are shown in bold.**

APPEARS THIS WAY
ON ORIGINAL

Table 25 Summary of Maximum Individual Responses to the Question 'Would You Chew This Gum Just to Get the Drug Effect?'

SUBJECT	ACTIVE ORIG GUM	[illegible]
1	NO	NO
2	NO	NO
3	SOME	SOME
4	NO	NO
7	SOME	SOME
8	A LOT	NO
9	A LOT	NO
11	NO	NO
12	SOME	SOME
14	A LOT	SOME
15	NO	NO
16	NO	NO
18	A LOT	NO
20	SOME	NO
22	NO	NO
24	NO	NO
106	NO	NO
117	NO	NO
119	NO	NO
121	NO	NO
123	NO	NO
205	NO	NO
210	SOME	NO
313	NO	NO

Responses to the question "Would you chew this gum just to get the drug effect?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. **Subject Numbers for Younger subjects are shown in bold.** Individual numeric responses are shown in the appendix.

Table 26 Maximum Individual Responses To The Question "How Sweet Is The Gum?"

SUB #	MINT PLACEBO	ORIG 2MG	ORIG 4MG	ORIG 6MG	ORIG PLACEBO
1	48	8	1	0	11
2	81	[illegible]	[illegible]	4	4
3	26	[illegible]	[illegible]	22	2
4	78	[illegible]	[illegible]	0	54
7	60	[illegible]	7	21	17
8	21	[illegible]	[illegible]	8	4
9	1	[illegible]	[illegible]	1	1
11	42	[illegible]	[illegible]	2	44
12	61	[illegible]	22	5	53
14	72	[illegible]	[illegible]	18	41
15	61	[illegible]	[illegible]	0	82
16	0	[illegible]	[illegible]	38	3
18	30	[illegible]	[illegible]	1	60
20	37	[illegible]	[illegible]	28	40
22	14	[illegible]	[illegible]	8	0
24	0	[illegible]	[illegible]	0	0
106	48	[illegible]	[illegible]	0	0
117	76	[illegible]	23	21	3
119	43	[illegible]	22	20	80
121	7	[illegible]	[illegible]	0	5
123	16	[illegible]	[illegible]	0	24
205	8	[illegible]	[illegible]	0	0
210	77	[illegible]	[illegible]	10	0
313	0	[illegible]	[illegible]	35	4

Table made by the reviewer from the sponsor's SAS data set (GUMALLT). Responses ranged from "Not at all"=0 to "Extremely"=100. **Subject numbers for younger subjects are shown in bold.**

Table 27 Summary of Maximum Individual Responses to the Question 'How Sweet is the Gum?'

SUBJECT	ACTIVE ORIG GUM FLAVOR	
1	NO	NO
2	NO	NO
3	NO	NO
4	NO	SOME
7	SOME	NO
8	NO	NO
9	NO	NO
11	SOME	SOME
12	NO	NO
14	NO	NO
15	NO	NO
16	SOME	NO
18	NO	NO
20	SOME	SOME
22	NO	NO
24	NO	NO
106	NO	NO
117	NO	NO
119	NO	A LOT
121	NO	NO
123	NO	NO
205	NO	NO
210	NO	NO
313	SOME	NO

Responses to the question "How sweet is the gum?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. **Subject Numbers for Younger subjects are shown in bold.**

Table 28 Maximum Individual Responses To The Question "How Much Do You Like The Gum Overall?"

SUB #	MINT PLACEBO	[illegible]	ORIG 4MG	ORIG 8MG	ORIG PLACEBO
1	0	[illegible]	[illegible]	0	0
2	47	[illegible]	[illegible]	3	7
3	9	[illegible]	[illegible]	20	43
4	70	[illegible]	[illegible]	0	54
7	50	[illegible]	[illegible]	54	28
8	75	[illegible]	[illegible]	21	3
9	1	[illegible]	[illegible]	90	1
11	27	[illegible]	[illegible]	37	40
12	66	[illegible]	[illegible]	21	32
14	71	[illegible]	[illegible]	69	32
15	80	[illegible]	[illegible]	0	61
16	4	[illegible]	[illegible]	0	3
18	79	[illegible]	[illegible]	0	69
20	34	[illegible]	[illegible]	11	58
22	4	[illegible]	[illegible]	0	0
24	0	[illegible]	[illegible]	0	0
106	100	[illegible]	[illegible]	0	62
117	56	[illegible]	[illegible]	0	0
119	1	[illegible]	[illegible]	0	49
121	0	[illegible]	[illegible]	0	0
123	15	[illegible]	[illegible]	0	1
205	0	[illegible]	[illegible]	0	0
210	10	[illegible]	[illegible]	52	21
313	0	[illegible]	[illegible]	0	0

Table made by the reviewer from the sponsor's SAS data set (GUMALLT). Responses ranged from "Not at all"=0 to "Extremely"=100. **Subject numbers for younger subjects are shown in bold.**

APPEARS THIS WAY
ON ORIGINAL

Table 29 Summary of Maximum Individual Responses to the Question How Much Do You Like the Gum Overall?

SUBJ #	ACTIVE ORIG GUM	ORIG FLAVOR
1	NO	NO
2	NO	NO
3	SOME	SOME
4	NO	SOME
7	SOME	SOME
8	NO	NO
9	A LOT	NO
11	SOME	SOME
12	SOME	SOME
14	A LOT	SOME
15	NO	SOME
16	NO	NO
18	NO	SOME
20	SOME	SOME
22	NO	NO
24	NO	NO
106	SOME	SOME
117	NO	NO
119	NO	SOME
121	NO	NO
123	NO	NO
205	NO	NO
210	SOME	NO
313	NO	NO

Responses to the question "How much do you like the gum overall?" were recorded on a 100mm VAS for each treatment condition. These results were summarized by the reviewer as follows: Scores of <25 were coded as NO, scores of 25 to 75 were coded as SOME, scores of >75 were coded as A LOT. For the active Nicorette treatment conditions, the highest response from the 2, 4, and 8mg conditions was used to determine the maximum liking score. **Subject Numbers for Younger subjects are shown in bold.**

14. Appendix 2: FoxPro Computer Program For Analysis Of Data From Study MD01011

To create the tables in Appendix 1, the maximum responses across time for each subject for each treatment condition were extracted from the sponsor's dataset using an excel pivot table. The maximum responses across doses was categorized using the following FoxPro program. Data from confectionery and fruit flavored gum was taken directly from the excel pivot tables.

```
GO TOP
DO WHILE NOT EOF()
DO CASE
CASE MINT2MG<25 AND MINT4MG<25 AND MINT8MG<25
REPLACE MINTNIC WITH 'NO'
CASE MINT2MG>75 OR MINT4MG>75 OR MINT8MG>75
REPLACE MINTNIC WITH 'LOTS'
CASE (MINT2MG=>25 AND MINT2MG<=75) OR (MINT4MG>=25 AND MINT4MG<=75)
OR (MINT8MG>=25 AND MINT8MG<=75)
REPLACE MINTNIC WITH 'SOME'

OTHERWISE
REPLACE MINTNIC WITH 'ERR'
ENDCASE

DO CASE
CASE ORIG2MG<25 AND ORIG4MG<25 AND ORIG8MG<25
REPLACE ORIGNIC WITH 'NO'
CASE ORIG2MG>75 OR ORIG4MG>75 OR ORIG8MG>75
REPLACE ORIGNIC WITH 'LOTS'
CASE (ORIG2MG=>25 AND ORIG2MG=<75) OR (ORIG4MG>=25 AND ORIG4MG<=75)
OR (ORIG8MG>=25 AND ORIG8MG=<75)
REPLACE ORIGNIC WITH 'SOME'
OTHERWISE
REPLACE ORIGNIC WITH 'ERR'
ENDCASE

DO CASE
CASE ORIGPLACEB<25
REPLACE ORIGFLAVOR WITH 'NO'
CASE (ORIGPLACEB>=25 AND ORIGPLACEB=<75)
REPLACE ORIGFLAVOR WITH 'SOME'
CASE ORIGPLACEB>75
REPLACE ORIGFLAVOR WITH 'LOTS'
```

```
OTHERWISE
REPLACE ORIGFLAVOR WITH 'ERR'
ENDCASE

DO CASE
CASE MINTPLACEB<25
REPLACE MINTFLAVOR WITH 'NO'
CASE (MINTPLACEB>=25 AND MINTPLACEB=<75)
REPLACE MINTFLAVOR WITH 'SOME'
CASE MINTPLACEB>75
REPLACE MINTFLAVOR WITH 'LOTS'
OTHERWISE
REPLACE MINTFLAVOR WITH 'ERR'
ENDCASE

DO CASE
CASE AMPHETMINT<25
REPLACE MINTAMP WITH 'NO'
CASE (AMPHETMINT>=25 AND AMPHETMINT<=75)
REPLACE MINTAMP WITH 'SOME'
CASE AMPHETMINT>75
REPLACE MINTAMP WITH 'LOTS'
OTHERWISE
REPLACE MINTAMP WITH 'ERR'
ENDCASE

DO CASE
CASE AMPHETORIG<25
REPLACE ORIGAMP WITH 'NO'
CASE (AMPHETORIG>=25 AND AMPHETORIG<=75)
REPLACE ORIGAMP WITH 'SOME'
CASE AMPHETORIG>75
REPLACE ORIGAMP WITH 'LOTS'
OTHERWISE
REPLACE ORIGAMP WITH 'ERR'
ENDCASE

SKIP
ENDDO
```