

Low-Nitrosamine Dissolvable Tobacco Products

Star Scientific, Inc.

Part III

Initiation and Cessation



Using science to reduce tobacco-related harm
at every level of the population

Summary - Parts I & II

So far, Star has described how the ARIVA and STONEWALL products were developed to have very low nitrosamine content, very low polycyclic aromatic hydrocarbon content, and a controlled nicotine content and delivery.

Star has also described how the nicotine content, flavor, packaging, marketing and promotion were designed to appeal to adult smokers.

Star has presented data from truly independent researchers showing that the comparative desirability of the products is less than for the typical OTC NRT products and a number of other PREPS with higher nicotine loadings.

Subjective Effects

Star Clinical Study SSI-040:

- Star has completed one sponsored study of STONEWALL versus Commit lozenges and matched placebos.
- The study was done with the hypothesis that STONEWALL might be more effective in reducing craving than Commit.

SSI-040 Study Subjects

Volunteer cigarette smokers participated in a taste and flavor study where they were held abstinent for about 1-2 hours, then tried each active or matching placebo in a two-session cross-over Latin Square design.

Male	21 (44%)
Female	27 (56%)
Age (mean age in years)	47.3
Mean Years Smoking	31.0
Mean Fagerström Score	6.7
URICA Scores	
Pre-contemplation	2.1
Contemplation	4.0
Preparing for Action	3.3
Maintenance	3.3
Readiness for Change	8.5

SSI-040 Craving

Primary QSU Outcome (mean, SD)

	Pre-Treatment	Post-Treatment	(Active v. Placebo)
STONEWALL	40.7 (16)	33.5 (14)	p< 0.0012
Commit	41.0 (16)	32.6 (14)	p< 0.0005
Stonewall PLC	42.9 (16)	39.4 (16)	
Commit PLC	41.7 (17)	38.8 (16)	

Primary MBRS Outcome (Questions 1-7, mean, SD)

	Pre-Treatment	Post-Treatment	(Active v. Placebo)
STONEWALL	7.5 (6.2)	5.2 (5.7)	p< 0.002
Commit	7.0 (6.1)	4.9 (4.9)	p< 0.009
Stonewall PLC	7.7 (6.3)	7.3 (6.9)	
Commit PLC	6.9 (6.2)	6.5 (6.5)	

SSI-040 Adverse Events

Adverse Events (ITT population, N=112)

	STONEWALL	Commit	SW Plc	Commit Plc
Headache	0	0	1	0
Nausea	<u>3</u>	<u>7</u>	<u>1</u>	<u>0</u>
Dyspepsia	<u>3</u>	<u>3</u>	<u>0</u>	<u>1</u>
Dry Mouth	0	1	0	0
Eructation	1	0	0	0
Vomiting	0	1	0	0
Paresthesia (Mouth Burning)	<u>3</u>	<u>5</u>	<u>0</u>	<u>0</u>
Dizziness	0	1	0	0
Hypesthesia	1	0	0	0
Hiccup	<u>4</u>	<u>2</u>	<u>1</u>	<u>0</u>
Pharyngitis	0	3	0	0
Cough	0	1	0	0

Why Do Purchasers Try ARIVA and STONEWALL?

Percent

Why Used

No smoking area	30
Switch to it	23
Try to cut down	16
Try to quit	19

How Learned of Product

Friend	35
Store Display	39
Advertising	16
Internet/Other	10

Perceptions and Properties

Caraballo et al. (2006), conducted a series of 16 focus groups in an exploratory study of PREP products on the market in 2002 (Eclipse, Omni, Advance, Accord, ARIVA).

The purpose was to find out how individuals learned of PREPS, if they had tried PREPS, and what their experience had been.

140 individuals who had smoked one or more cigarettes a day in the last month, smoked 100 cigarettes in their lifetime, and who had ever tried a PREP were recruited.

Most learned of PREPS through advertising, family or friends, tried them to lower risk or through curiosity and did not like them.

Survey Studies

O'Hegarty et al. (2007), conducted a nested study of PREP marketing in the Caraballo study previously cited.

The authors found that smokers responded to all of the factors that had previously been found to be important in tobacco marketing (color, attractiveness, layout, images, message, health implications).

Their conclusion was that the same elements that govern general tobacco marketing govern PREP promotion.

Conclusions - Initiation

ARIVA and STONEWALL initiation is by smokers and SLT users in the 35-50+ year age group who are attracted by curiosity. Most initiation is peer-to-peer and by store display.

Multiple previously cited studies (Parts I & II) and the sales data show that the products have low uptake, with many new users (smokers) finding the product mildly aversive on first use.

There has been no adolescent use or market uptake reported to the company in 10 years (Star Safety Department experience), confirmed by the AAPCC data.

Migration

ARIVA (the smoker's product) is loaded at 1.5 mg nicotine at pH 7.5.

STONEWALL (the SLT user's product) is loaded at 4.0 mg nicotine at pH 7.5.

Most light to moderate smokers select ARIVA.

Most heavy smokers and SLT users select STONEWALL.

Usage data suggests most users are using 4-6 lozenges a day.

We do not know how much dual use there is, though the survey data suggest that most dual use is in environments where smoking is prohibited or to avoid exposing others to smoke (work, public places, cars) with significantly fewer cigarettes smoked by users.

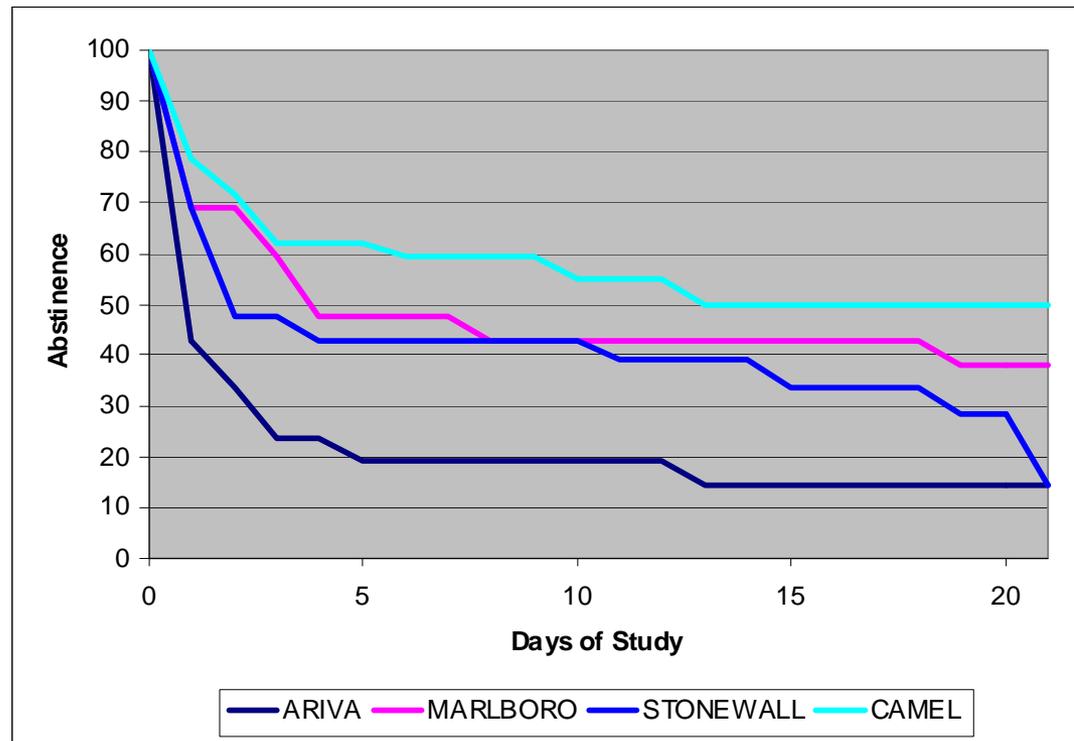
We do not know how many users are successful in cessation using the product, but clearly some are using it to cut down on smoking and some to quit smoking.

The one cessation study reported (Hatsukami 2011) is interesting.

Hatsukami et al. 2011

Hatsukami et al. recruited smokers motivated to quit, allowed them to test four PREPs, then had them attempt cessation using the PREP of their choice. 97 of 135 initially recruited entered the survival phase; selection was roughly equal across three of the PREPS studied (General Snus was not selected by any).

ARIVA was least effective in supporting cessation, with rank order for the rest roughly proportional to mg total CDC nicotine.



ARIVA (1.5) < STONEWALL (4.0) < Marlboro (5.4) < Camel (5.6)

Migration

Two other recent studies involving Star dissolvable tobacco products in populations of smokers not motivated or planning to quit have also provided interesting results related to migration and cessation.

Carpenter and Gray (2010) found that relative to a control group (conventional cigarettes), daily use of ARIVA and STONEWALL for 2 weeks resulted in:

- A statistically significant reduction (40%) in cigarettes smoked per day;
- Significant increases in two measures of readiness to quit in the next month ($p < 0.001$), or within the next six months ($p = 0.04$); and,
- Significant increases in self-efficacy to quit smoking ($p < 0.001$).

Migration

O'Connor et al. (2011) found that smokers not willing to quit may be willing to use an oral smokeless product such as STONEWALL as a substitute for cigarettes, but did not quit completely (suggesting dual use with fewer cigarettes smoked in this population).

The same was true for the NRT comparator used in this study, Commit lozenge.

Results showed:

- A statistically significant reduction (25%) in cigarettes per day
- Exhaled CO decreased significantly (10%) from before to after trial
- Salivary cotinine was stable

Smokers smoked less, and compensated for nicotine needs with the reduced toxin content oral products.

How Bad is Dual Use?

There is a problem with the “dual use” data in the literature.

There are few data on dual use of low-nitrosamine products in the US, since there is little use of low-nitrosamine products in the US.

Studies of dual use in Sweden, the only country where there is high population prevalence of users of low-nitrosamine products have not shown an increased risk for dual use relative to smoking.

The open question is how much, if any, benefit is experienced by “dual users” of low-nitrosamine products relative to continuing smoking alone, remembering that “dual users” of dissolvable products smoke significantly fewer cigarettes.

Remember, the makers of low-nitrosamine products do not claim that there is any such health benefit.

Smoking Cessation

A panel of experts convened to predict the potential impact of a low-nitrosamine smokeless tobacco (LN-SLT) product such as ARIVA or snus on cigarette smoking in the US concluded:

*“An overall consensus was reached that the introduction of a new LN-SLT product introduced to the US market under strict regulations but with relevant health claims would **not** impede the decline in overall smoking prevalence.”*

Indeed, all panel members indicated that the new policy would likely accelerate the decline in smoking prevalence.

“...the results from this study indicate that the introduction of a well regulated LN-SLT product is expected to reduce smoking and only modestly increase SLT use in the United States. Notably, the overall impact of the new policy regime is predicted to lead to virtually no change in overall tobacco use...”

Effects on Cigarette Use

Multiple peer-reviewed publications have reported that use of snus and other SLT products do not significantly contribute to smoking initiation, may be protective against smoking, and may be useful for smoking cessation. Some examples:

As previously noted, smoking rates for Swedish men have plummeted since the 1970s as snus use has increased (e.g. see Foulds et al. 2003).

Furberg et al. (2005) found that regular snus use was associated with smoking cessation, not initiation, among almost 15,000 male participants in the Swedish Twin Registry (STR). Regular and occasional snus use was protective against ever smoking.

Furberg et al. (2008) found that snus use was the strongest independent correlate of smoking cessation in a sample of 14,715 male and female smokers in the STR.

Ramström and Foulds (2006) conducted a retrospective analysis of data from a cross-sectional survey of 6,752 adult Swedes from 2001-2002, and found that use of snus was associated with a reduced risk of becoming a daily smoker, and an increased likelihood of stopping smoking.

Where the *Real* Issue is

Forty years ago the major US tobacco companies launched a marketing campaign to replace unfiltered cigarettes with filtered cigarettes.

The effect was to replace unfiltered with filtered cigarettes.

Thirty years ago saw the start of the “TAR and NICOTINE” wars where companies started marketing “light” cigarettes.

The effect was to increase the population exposure to tobacco toxins.

Twenty years ago saw the start of the proposed development of PREP products that filtered, heated, and otherwise altered nicotine delivery.

Effects have been minimal to date.

The moral is that **WHAT** is said about these products and **HOW** it is said matters a great deal.

Star's Recommendations

Dissolvable products are a “safe” place for the Agency to experiment with tobacco content, purity standards and labeling.

Star thinks tobacco products should be required to be labeled with their nicotine and major toxin levels. We know enough to start doing something.

For smokeless products these are TSNAs and Benzo[a]pyrene*.

Levels of these toxins should be clearly shown in standard units per unit of use, as well as per mg of nicotine, the desired psychoactive constituent.

We think there should be standards for toxin content that meet or exceed the WHO standards, as previously described.

*Benzo[a]pyrene is not the only toxic PAH, but is the most well-known and potent carcinogen and is a marker for other PAH toxins.

Sample Labeling

Example of a Proposed Dissolvable Tobacco Product Label

Tobacco Facts		
Portion Size: One lozenge		
Portions per package: 20		
Nicotine	4 mg per lozenge	
	Per Lozenge	Per mg Nicotine
Tobacco Specific Nitrosamines	xx PPB	yy PPB
NNN	xx PPB	yy PPB
NNK	xx PPB	yy PPB
Polycyclic Aromatic Hydrocarbons		
Benzo(a) Pyrene	xx PPB	yy PPB

Conclusion

- Tobacco is toxic and can never be made “safe”
- Tobacco is addicting and will always be so
- There is no “safe” tobacco product

But some products are more toxic than others.

The US Surgeon General said it best in 2000:

“As with all other consumer products, adult users of tobacco should be fully informed of the products’ ingredients and additives and of any known toxicity when used as intended. Additionally, as with other consumer products, the manufactured tobacco product should be no more harmful than necessary given available technology.”