22nd Century Limited, LLC

IND 103589

September 28, 2012

Bob Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and
Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND 103589 (SN004) X-22 Smoking Cessation Product
Annual Report

Dear Dr. Rappaport,

Reference is made to our Initial IND 103,589 for X-22 Smoking Cessation Product, submitted June 21, 2011 (SN000), for our investigational product X-22 Smoking Cessation Product for the indication of smoking cessation.

We are submitting herewith the Annual Report for the period July 27, 2011 to September 1, 2012 for this IND.

If you have additional questions or require further information, please do not hesitate to contact me by e-mail at (b) (6), (b) (4) or by telephone at (b) (6), (b) (4)

Kind regards,

(b) (6), (b) (4)

Regulatory Affairs Consultant

9530 Main Street, Clarence, New York 14031 • TEL 716-270-1523 • FAX 716-877-3064 • www.xxiicentury.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: May 31, 2009
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
22nd Century Limited, LLC

2. DATE OF SUBMISSION
09/28/2012

3. ADDRESS *(Number, Street, City, State and Zip Code)*
9530 Main Street
Clarence, New York 14031

4. TELEPHONE NUMBER *(Include Area Code)*
(b) (4), (b) (6)

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
X-22 Smoking Cessation Product

6. IND NUMBER *(If previously assigned)*
103589

7. INDICATION(S) *(Covered by this submission)*
Smoking cessation

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☑ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
IND # 69,185 (Letter of cross-reference submitted in Initial IND)

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER: 4

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☑ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- [x] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [x] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [x] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [x] 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- [ ] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [x] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [x] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [x] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [x] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [x] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [ ] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [x] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [x] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [ ] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☑ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☑ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Michael R. Moynihan, Ph.D.

VP Research and Development, 22nd Century Limited, LLC

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

(b) (4), (b) (6)

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

(b) (4), (b) (6)
Regulatory Affairs Consultant for 22nd Century

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

(b) (4), (b) (6)

18. ADDRESS *(Number, Street, City, State and Zip Code)*

(b) (4), (b) (6)

19. TELEPHONE NUMBER *(Include Area Code)*

(b) (4), (b) (6)

20. DATE

09/28/2012

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

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9530 Main Street
Clarence, NY 14031
(716) 270-1523

2012 IND ANNUAL REPORT

IND No.:	103,589
Serial No.:	004
Product Name:	X-22 Smoking Cessation Product
Indication:	Smoking Cessation
Reporting Period:	27 July 2011 to 01 September 2012
Date of Report:	27 Sep 2012

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1 INDIVIDUAL STUDY INFORMATION

One clinical study of X-22 Smoking Cessation Product (X-22), Study X-22-201, was active during the reporting period. Table 1 summarizes the status of IND studies.

Table 1 IND Studies

Protocol Number	Title	No. Planned/ Entered	Demographics			No. Completed/ Discontinued	Study Status
			Subject Age Range (years)	Gender	Race		
X-22-201	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	216/234	20-65	128 M 106 F	169 W 59 B 3 A 3 O	175/59	Completed

Abbreviations: A=Asian, B=Black, F=female, M=male, O=other, W=white
Source: X-22-201 Table 14.1.1.2

1.1 Studies in Progress

There are no IND studies currently in progress.

1.2 Completed Studies

One clinical study was completed during this reporting period, Study X-22-201. The clinical study report is in preparation and will be submitted to the FDA when available.

Study X-22-201

Title: 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

Objectives: The primary objective of this study was to evaluate the efficacy of X-22 as a smoking cessation aid.

Secondary objectives of the study included:

- To assess the effect of X-22 on abstinence at 2 and 3 months after the quit date,
- To assess withdrawal symptoms,
- To evaluate the effect of X-22 on cigarette consumption prior to the quit date, and
- To evaluate the tolerability of X-22 as a smoking cessation aid.

Exploratory objectives included:

- To evaluate other factors that may have an influence on the efficacy of X-22 as a smoking cessation aid, including subject gender, results of a Sensory Questionnaire prior to the quit date, and results of the Fagerström Test of Nicotine Dependence prior to the quit date.
- To compare nicotine use between groups over time.

Description of Subject Population: Healthy male and female adult smokers who planned to quit smoking.

Study Design: This was a prospective, randomized, multicenter, double-blind, parallel, active controlled, Phase II clinical trial in which healthy smokers were enrolled and followed over approximately 19 weeks. At the beginning of the treatment phase, subjects were randomized in a 1:1 ratio to receive either X-22 Smoking Cessation Product, or active control cigarettes, and switched from smoking their regular brand to the assigned study cigarettes at that time. Subjects smoked the study cigarettes ad libitum for 6 weeks prior to the quit date. After the quit date, subjects were instructed to abstain from smoking or using any tobacco product and were evaluated for safety and efficacy during a 4-week abstinence phase and 4 week follow-up phase.

Status of Study: Completed

Brief Summary of Results:

Safety Results: A total of 234 subjects were enrolled in this study (118 in the X-22 group and 116 in the control group). Subjects in the X-22 group smoked study cigarettes for a mean of 5.64 weeks and subjects in the control group smoked study cigarettes for a mean of 5.85 weeks. Of the 234 enrolled subjects, 175 completed, 59 discontinued. Of the 59 subjects who discontinued from the study, 3 discontinued because of an adverse event (AE), 1 died, 29 were lost to follow-up, 1 was noncompliant, 1 was discontinued by the sponsor for noncompliance, 1 subject had to discontinue due to incarceration, and 23 subjects withdrew consent.

A total of 118 subjects experienced an AE during this study (60 in the X-22 group and 58 in the control group). Most AEs were mild or moderate in severity; 10 subjects in the X-22 group and 11 subjects in the control group experienced severe AEs.

The most frequently reported adverse events were in the body systems of infections and infestations (62 events; 31 in the X-22 group and 31 in the control group), respiratory, thoracic and mediastinal disorders (26 events; 11 in the X-22 group and 15 in the control group), gastrointestinal disorders (22 events; 11 in the X-22 group and 11 in the control group), and nervous system disorders (20 events: 11 in the X-22 group and 9 in the control group). Overall, AEs were reported at similar frequencies in the X-22 and control groups across body systems.

Five of the AEs in the X-22 group and 1 in the control group were serious adverse events (SAEs). Two of the AEs in the X-22 group and none in the control group led to discontinuation of the investigational product. One subject (Subject 3022) died as a result of an SAE. The investigator determined that the event was not related to what was later determined to be the active control cigarette. A brief summary of each SAE is provided below in Section 2.2.

Pharmacokinetic Results:

No pharmacokinetic results are available at this time. Analysis of the cotinine data from Trial X-22-201 is ongoing.

1.3 Foreign or other Clinical Trials Conducted by 22nd Century Limited, LLC Not Conducted Under IND 103,589.

There are no clinical trials of X-22 Smoking Cessation Product being conducted outside of the United States.

1.4 Non-22nd Century Limited, LLC Sponsored Studies

There are no clinical trials of the X-22 Smoking Cessation Product being conducted by sponsors other than 22nd Century Limited, LLC. A number of independent smoking cessation studies have been carried out recently with other very low nicotine (VLN) cigarettes.

A study involving 1410 subjects led by Dr. Linda Walker at the University of Auckland Clinical Trials Research Unit compared the use of VLN cigarettes and nicotine replacement therapy (NRT; nicotine patches, and/or nicotine gums or nicotine lozenges) to the use of NRT alone (Walker et al, 2012). The VLN cigarette used in this study was reported to have yields of $\leq$0.05 mg nicotine and 4 mg "tar" per cigarette. Subjects in the VLN + NRT cigarette arm were instructed to smoke the VLN cigarettes ad libitum whenever they had an urge to smoke during the 6 weeks following their target quit date. The primary endpoint, 7-day point-prevalence smoking abstinence 6 months after the quit day, was significantly higher in the VLN + NRT cigarette group, 33% versus 28%, p = 0.037. Continuous abstinence was also higher in the VLN cigarette group, 23% versus 15%, p = 0.0003.

Two additional studies used Xodus® VLN cigarettes, a commercial cigarette developed by 22nd Century Limited, LLC that is no longer marketed. Xodus was made with tobacco from the same very low alkaloid tobacco variety as X-22 and had yields of 0.09 mg nicotine and 10 mg "tar" per cigarette under the International Organization for Standardization (ISO) smoking regimen.

A study involving 219 subjects led by Dr. Dorothy Hatsukami at the University of Minnesota evaluated the effect of the combination use of a 21 mg nicotine patch and VLN cigarettes compared to use of VLN cigarettes alone or 21 mg nicotine patch alone on abstinence and withdrawal (NCT01050569). The study has been completed but results have not yet been released.

A study involving 200 subjects led by Dr. Hayden McRobbie at the Queen Mary University of London evaluated the use of VLN cigarettes for 2 weeks after their quit date in combination with varenicline (Chantix®) or NRT compared to use of Chantix alone or NRT alone (NCT01250301). The study has been completed but results have not been released.

22nd Century is providing the National Institute on Drug Abuse (NIDA) with SPECTRUM® research cigarettes that have various levels of nicotine content in the tobacco filler (from very low to high) for NIDA's ongoing research on how different nicotine levels in cigarettes affect smoking behavior and the results of smoking.

2 SUMMARY INFORMATION

X-22-201 was the only clinical trial active during this reporting period. A summary of the safety information obtained in Study X-22-201 is provided in this section.

2.1 Adverse Events by Body System

A summary of AEs by body system is presented in Table 2. A total of 114 subjects experienced an AE during this study (58 in the X-22 group and 56 in the control group). The most frequently reported adverse events were in the body systems of infections and infestations (62 events; 31 in the X-22 group and 31 in the control group), respiratory, thoracic and mediastinal disorders (26 events; 11 in the X-22 group and 15 in the control group), gastrointestinal disorders (22 events; 11 in the X-22 group and 11 in the control group), and nervous system disorders (20 events: 11 in the X-22 group and 9 in the control group). Overall, AEs were reported at similar frequencies in the X-22 and control groups across body systems.

Table 2 Adverse Events in Study X-22-201 by System Organ Class and Preferred Term

22nd Century Limited, LLC. Page 1 of 6

Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	X-22 Smoking Cessation Product (N=106)	Active Control Cigarettes (N=110)	Total (N=216)
Any Adverse Event	58 (54.7)	56 (50.9)	114 (52.8)
Blood and lymphatic system disorders	1 (0.9)	2 (1.8)	3 (1.4)
Blood disorder	0	1 (0.9)	1 (0.5)
Leukocytosis	1 (0.9)	0	1 (0.5)
Lymphadenopathy	0	1 (0.9)	1 (0.5)
Ear and labyrinth disorders	0	2 (1.8)	2 (0.9)
Ear pain	0	1 (0.9)	1 (0.5)
Tympanic membrane perforation	0	1 (0.9)	1 (0.5)
Endocrine disorders	1 (0.9)	1 (0.9)	2 (0.9)
Hypothyroidism	1 (0.9)	1 (0.9)	2 (0.9)
Eye disorders	2 (1.9)	2 (1.8)	4 (1.9)
Astigmatism	1 (0.9)	0	1 (0.5)
Dark circles under eyes	1 (0.9)	0	1 (0.5)
Myopia	1 (0.9)	0	1 (0.5)
Retinal disorder	0	1 (0.9)	1 (0.5)
Visual impairment	0	1 (0.9)	1 (0.5)
Gastrointestinal disorders	11 (10.4)	11 (10.0)	22 (10.2)
Abdominal discomfort	0	1 (0.9)	1 (0.5)
Abdominal hernia obstructive	1 (0.9)	0	1 (0.5)
Abdominal pain lower	0	1 (0.9)	1 (0.5)

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Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	X-22 Smoking Cessation Product (N=106)	Active Control Cigarettes (N=110)	Total (N=216)
Abdominal pain upper	0	2 (1.8)	2 (0.9)
Constipation	0	4 (3.6)	4 (1.9)
Diarrhoea	1 (0.9)	0	1 (0.5)
Dyspepsia	2 (1.9)	0	2 (0.9)
Food poisoning	2 (1.9)	0	2 (0.9)
Gingival bleeding	0	1 (0.9)	1 (0.5)
Gingivitis	1 (0.9)	0	1 (0.5)
Nausea	2 (1.9)	1 (0.9)	3 (1.4)
Oral pain	1 (0.9)	0	1 (0.5)
Tooth loss	0	1 (0.9)	1 (0.5)
Toothache	0	1 (0.9)	1 (0.5)
Vomiting	2 (1.9)	0	2 (0.9)
General disorders and administration site conditions	3 (2.8)	1 (0.9)	4 (1.9)
Chest pain	1 (0.9)	1 (0.9)	2 (0.9)
Irritability	1 (0.9)	0	1 (0.5)
Pyrexia	1 (0.9)	0	1 (0.5)
Immune system disorders	0	1 (0.9)	1 (0.5)
Seasonal allergy	0	1 (0.9)	1 (0.5)
Infections and infestations	30 (28.3)	31 (28.2)	61 (28.2)
Abscess	1 (0.9)	0	1 (0.5)
Bronchitis	1 (0.9)	2 (1.8)	3 (1.4)
Cellulitis	1 (0.9)	0	1 (0.5)

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Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	X-22 Smoking Cessation Product (N=106)	Active Control Cigarettes (N=110)	Total (N=216)
Ear infection	0	1 (0.9)	1 (0.5)
Gastroenteritis viral	0	1 (0.9)	1 (0.5)
Groin abscess	0	1 (0.9)	1 (0.5)
Influenza	1 (0.9)	0	1 (0.5)
Kidney infection	0	1 (0.9)	1 (0.5)
Laryngitis	2 (1.9)	0	2 (0.9)
Localised infection	1 (0.9)	0	1 (0.5)
Lower respiratory tract infection	0	2 (1.8)	2 (0.9)
Nasopharyngitis	19 (17.9)	17 (15.5)	36 (16.7)
Oral herpes	0	1 (0.9)	1 (0.5)
Osteomyelitis	0	1 (0.9)	1 (0.5)
Pharyngitis	0	1 (0.9)	1 (0.5)
Pneumonia	0	1 (0.9)	1 (0.5)
Post procedural infection	1 (0.9)	0	1 (0.5)
Sepsis	0	1 (0.9)	1 (0.5)
Sinusitis	2 (1.9)	3 (2.7)	5 (2.3)
Tooth infection	3 (2.8)	0	3 (1.4)
Upper respiratory tract infection	0	1 (0.9)	1 (0.5)
Urinary tract infection	0	1 (0.9)	1 (0.5)
Varicella	1 (0.9)	0	1 (0.5)
Injury, poisoning and procedural complications	9 (8.5)	4 (3.6)	13 (6.0)
Ear injury	1 (0.9)	0	1 (0.5)
Excoriation	1 (0.9)	0	1 (0.5)
Eye injury	1 (0.9)	0	1 (0.5)
Foot fracture	0	1 (0.9)	1 (0.5)

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Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	X-22 Smoking Cessation Product (N=106)	Active Control Cigarettes (N=110)	Total (N=216)
Head injury	2 (1.9)	0	2 (0.9)
Joint sprain	2 (1.9)	1 (0.9)	3 (1.4)
Laceration	3 (2.8)	0	3 (1.4)
Limb injury	0	1 (0.9)	1 (0.5)
Muscle strain	0	1 (0.9)	1 (0.5)
Procedural pain	1 (0.9)	0	1 (0.5)
Investigations	4 (3.8)	6 (5.5)	10 (4.6)
Blood carbon monoxide increased	1 (0.9)	0	1 (0.5)
Blood creatinine increased	0	1 (0.9)	1 (0.5)
Blood lactate dehydrogenase increased	0	1 (0.9)	1 (0.5)
Blood potassium increased	1 (0.9)	1 (0.9)	2 (0.9)
Blood pressure increased	1 (0.9)	2 (1.8)	3 (1.4)
Gamma-glutamyltransferase increased	1 (0.9)	1 (0.9)	2 (0.9)
Haematocrit decreased	0	1 (0.9)	1 (0.5)
Haemoglobin decreased	0	1 (0.9)	1 (0.5)
Red blood cell count decreased	0	1 (0.9)	1 (0.5)
Metabolism and nutrition disorders	3 (2.8)	0	3 (1.4)
Glucose tolerance impaired	1 (0.9)	0	1 (0.5)
Hypercholesterolaemia	1 (0.9)	0	1 (0.5)
Increased appetite	1 (0.9)	0	1 (0.5)
Vitamin D deficiency	1 (0.9)	0	1 (0.5)
Musculoskeletal and connective tissue disorders	5 (4.7)	3 (2.7)	8 (3.7)
Arthralgia	0	1 (0.9)	1 (0.5)

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22nd Century Limited, LLC.

Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	X-22 Smoking Cessation Product (N=106)	Active Control Cigarettes (N=110)	Total (N=216)
Back pain	1 (0.9)	0	1 (0.5)
Myalgia	1 (0.9)	0	1 (0.5)
Pain in extremity	2 (1.9)	2 (1.8)	4 (1.9)
Rheumatoid arthritis	0	1 (0.9)	1 (0.5)
Tendonitis	1 (0.9)	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9)	0	1 (0.5)
Uterine leiomyoma	1 (0.9)	0	1 (0.5)
Nervous system disorders	11 (10.4)	7 (6.4)	18 (8.3)
Dizziness	3 (2.8)	1 (0.9)	4 (1.9)
Dysgeusia	1 (0.9)	0	1 (0.5)
Headache	5 (4.7)	6 (5.5)	11 (5.1)
Nerve compression	0	1 (0.9)	1 (0.5)
Sinus headache	1 (0.9)	1 (0.9)	2 (0.9)
VIIth nerve paralysis	1 (0.9)	0	1 (0.5)
Psychiatric disorders	3 (2.8)	5 (4.5)	8 (3.7)
Alcoholism	1 (0.9)	0	1 (0.5)
Anxiety	2 (1.9)	0	2 (0.9)
Attention deficit/hyperactivity disorder	0	2 (1.8)	2 (0.9)
Depression	0	1 (0.9)	1 (0.5)
Insomnia	0	2 (1.8)	2 (0.9)
Reproductive system and breast disorders	0	1 (0.9)	1 (0.5)

Table Generation: 24AUG12 10:12 Program source: T_ae.sas

22nd Century Limited, LLC.

Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	X-22 Smoking Cessation Product (N=106)	Active Control Cigarettes (N=110)	Total (N=216)
Menorrhagia	0	1 (0.9)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	11 (10.4)	15 (13.6)	26 (12.0)
Cough	7 (6.6)	7 (6.4)	14 (6.5)
Dysphonia	0	1 (0.9)	1 (0.5)
Increased upper airway secretion	1 (0.9)	0	1 (0.5)
Nasal congestion	5 (4.7)	3 (2.7)	8 (3.7)
Oropharyngeal pain	0	5 (4.5)	5 (2.3)
Respiratory tract congestion	2 (1.9)	2 (1.8)	4 (1.9)
Rhinorrhoea	0	2 (1.8)	2 (0.9)
Throat irritation	0	1 (0.9)	1 (0.5)
Upper-airway cough syndrome	0	3 (2.7)	3 (1.4)
Skin and subcutaneous tissue disorders	0	2 (1.8)	2 (0.9)
Dermatitis allergic	0	1 (0.9)	1 (0.5)
Pruritus	0	1 (0.9)	1 (0.5)
Vascular disorders	2 (1.9)	2 (1.8)	4 (1.9)
Hypertension	2 (1.9)	2 (1.8)	4 (1.9)

Table Generation: 24AUG12 10:12 Program source: T_ae.sas

Source: Study X-22-201, Table 14.3.2.1

2.2 Serious Adverse Events

A summary of SAEs reported during Study X-22-201 is presented in Table 3 and a description of each SAE is provided below. Five of the AEs in the X-22 group and 1 in the control group were SAEs.

- Subject 1049 (obstructive abdominal hernia). Subject 1049, a 47-year-old Caucasian female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind study cigarettes on 08 Aug 2011 and stopped on 26 Sep 2011. The patient had a medical history of previous hernia repair. On (b) (6) the patient developed severe abdominal pain while exercising and went to an emergency room later that day. The patient was admitted to the hospital and hernia repair surgery was completed on (b) (6). She was released on 14 Oct 2011. The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as resolved on 13 Oct 2011.
- Subject 1073 (traumatic coma). Subject 1073, a 37-year-old black female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind study cigarettes on 15 Sep 2011. On 22 Sep 2011, the site was notified by the subject's daughter that the subject had been in a motor vehicle accident on (b) (6), was hospitalized in an intensive care unit, had a brain injury, and was in a coma. No further information was available. The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as ongoing at the conclusion of the study.
- Subject 1083 (uterine leiomyoma). Subject 1083, a 33-year-old Caucasian female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind study cigarettes on 14 Sep 2011. The patient had an active history of dysmenorrhea at screening. On 22 Dec 2011, the study site was notified that the subject had uterine fibroid tumors and had elected to have a hysterectomy, requiring hospitalization. The start date of the event was reported as (b) (6). The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as resolved on 18 Dec 2011.
- Subject 2009 (alcoholism). Subject 2009, a 55-year-old Caucasian male, was enrolled in the study and randomized to the X-22 group. He began smoking the double-blind study cigarettes on 09 Aug 2011. The subject had a history of alcoholism from 1996 to 23 Aug 2010. On 20 Sep 2011, the subject notified the study site that he had admitted himself to (b) (6) for alcohol detox on (b) (6). He started drinking again on 04 Sep 2011. When he realized "what road he was traveling down" he decided to admit himself for detox. The start date of the event was reported as 04 Sep 2011. The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as resolved on 21 Sep 2011.
- Subject 2061 (head injury). Subject 2061, a 33-year-old Caucasian female, was enrolled in the study and randomized to the X-22 group. She began smoking the double-blind

study cigarettes on 14 Sep 2011 and stopped on 05 Oct 2011. On 13 Oct 2011, the study site was notified that the subject had been a passenger in a motor vehicle accident on (b) (6) She was admitted to a hospital on that date for severe head trauma and seizures. She was released on 12 Oct 2011. The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as not resolved on 12 Oct 2011.

- Subject 3022 (Sepsis). Subject 3022, a 42-year-old Caucasian Hispanic male, was enrolled in the study and randomized to the control group. He began smoking the double-blind study cigarettes on 14 Sep 2011. The study site received a telephone call from the subject's partner reporting that the subject had complained of bilateral leg numbness and was taken to the emergency room, where he died soon after. A follow-up report identified the cause of death as sepsis most likely secondary to pancreatitis. Diagnoses prior to death included paraplegia secondary to large intrathecal hematoma, subarachnoid hemorrhage (stable), hypertension (stable), substance abuse (specifically methamphetamine), chest pain (myocardial infarction ruled out), acute pancreatitis, and sepsis most likely due to acute pancreatitis. Subarachnoid hemorrhage also occurred during the hospitalization and may have contributed to the cause of death. The date of hospital admission was not provided. On 06 Oct 2011, the subject chose to receive comfort care only and ongoing antibiotic therapy was discontinued. He expired on the evening of 07 Oct 2011 (Study Day 23). The investigator determined that the event was serious, severe, and not related to the investigational product. The outcome of the event was reported as fatal on 07 Oct 2011.

Table 3 Summary of Serious Adverse Events in Study X-22-201

Table 14.3.2.1
Serious Adverse Events
ITT/Safety Population

System Organ Class Preferred Term	X-22 Smoking Cessation Product (N=118)	Active Control Cigarettes (N=116)	Total (N=234)
Any Serious Adverse Event	5 (4.2)	1 (0.9)	6 (2.6)
Gastrointestinal disorders	1 (0.8)	0	1 (0.4)
Abdominal hernia obstructive	1 (0.8)	0	1 (0.4)
Infections and infestations	0	1 (0.9)	1 (0.4)
Sepsis	0	1 (0.9)	1 (0.4)
Injury, poisoning and procedural complications	2 (1.7)	0	2 (0.9)
Head injury	1 (0.8)	0	1 (0.4)
Traumatic coma	1 (0.8)	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	0	1 (0.4)
Uterine leiomyoma	1 (0.8)	0	1 (0.4)
Psychiatric disorders	1 (0.8)	0	1 (0.4)
Alcoholism	1 (0.8)	0	1 (0.4)

Source: Study X-22-201 Table 14.3.2.1

2.3 IND Safety Reports

There were no IND Safety Reports submitted during this reporting period.

2.4 Deaths

One subject died of sepsis during this study. The investigator determined that the event was not related to, what was later determined to be, the active control cigarette. See Section 1.2, Completed Studies, for a summary of this event.

2.5 Discontinuations Due to Adverse Events

A total of 5 subjects discontinued the use of investigational product during Study X-22-201 due to an AE. A list of these subjects is provided below:

Subject Number	Treatment Group	Adverse Event
1047	X-22	Laryngitis
1073	X-22	Traumatic coma
2061	X-22	Head injury
2009	X-22	Alcoholism
3022	Control	Sepsis

2.6 Smoking Rates Over Time

The number of cigarettes smoked per week during the study is presented in Table 4. At Week 0 (Baseline), subjects in the X-22 group (n=118) reported having smoked an average of 126.3 of their usual brand cigarettes and subjects in the control group (n=116) reported having smoked an average of 123.8 of their usual brand cigarettes during the previous week. At Week 6 (Quit Date), subjects in the X-22 group (n=88) reported having smoked an average of 122.4 study cigarettes and subjects in the control group (n=100) reported having smoked an average of 139.3 study cigarettes during the previous week. These data indicate that there was no important difference in smoking rates during the study in the X-22 group compared to the control group and that use of the low nicotine X-22 cigarette was not associated with an increase in smoking over time. Further analysis of smoking data is ongoing.

2.7 New Information Pertinent to the Understanding of X-22 Action

No new information became available during this reporting period.

Table 4 Summary of Number of Cigarettes Smoked per Week During Study X-22-201 Treatment Period

22nd Century Limited, LLC. **Page 1 of 2**

Protocol: X-22-201

Table 12.2.18
Summary of Number of Cigarettes Smoked per Week during Treatment Period by Visit - ITT
ITT Population

Visit	X-22 Smoking Cessation Product (N=118)	Active Control Cigarettes (N=116)	Total (N=234)
Visit 2 - Day 0			
N	118	116	234
Mean (SD)	126.3 (38.9)	123.8 (38.8)	125.1 (38.8)
Median	122.7	116.7	120.9
Min, Max	46, 233	66, 264	46, 264
Q1, Q3	99, 150	97, 139	98, 146
Visit 3 - Week 2			
N	106	110	216
Mean (SD)	170.1 (77.6)	155.1 (64.4)	162.5 (71.4)
Median	155.3	142.0	150.8
Min, Max	44, 440	69, 531	44, 531
Q1, Q3	127, 203	117, 176	119, 187
Visit 4 - Week 4			
N	97	105	202
Mean (SD)	135.3 (75.6)	147.2 (64.0)	141.5 (69.9)
Median	124.3	138.1	132.0
Min, Max	0, 318	44, 554	0, 554
Q1, Q3	89, 182	110, 172	101, 176

Note: Includes all cigarettes smoked - both study and non-study cigarettes.
Note: Visits 6 and 7 are smoking cessation periods, study cigarettes were not dispensed.

Table Generation: 12SEP12 09:54 Program source: T_Cigs.sas

Table 12.2.18
Summary of Number of Cigarettes Smoked per Week during Treatment Period by Visit - ITT
ITT Population

Visit	X-22 Smoking Cessation Product (N=118)	Active Control Cigarettes (N=116)	Total (N=234)
Visit 5 - Week 6			
N	88	100	188
Mean (SD)	122.4 (69.7)	139.3 (51.3)	131.4 (61.0)
Median	118.7	131.0	129.8
Min, Max	0, 309	6, 320	0, 320
Q1, Q3	72, 172	110, 164	95, 167
Visit 6 - Week 8			
N	81	96	177
Mean (SD)	28.1 (34.8)	30.6 (34.9)	29.5 (34.7)
Median	14.0	19.0	15.4
Min, Max	0, 136	0, 158	0, 158
Q1, Q3	3, 42	5, 40	4, 41
Visit 7 - Week 10/Early Termination			
N	81	95	176
Mean (SD)	34.9 (42.7)	33.8 (37.5)	34.3 (39.9)
Median	18.1	23.7	21.3
Min, Max	0, 177	0, 169	0, 177
Q1, Q3	3, 49	4, 50	3, 49

Note: Includes all cigarettes smoked - both study and non-study cigarettes.
Note: Visits 6 and 7 are smoking cessation periods, study cigarettes were not dispensed.

Source: X-22-201 Table 12.2.18

3 NONCLINICAL STUDIES

3.1 Pharmacology

3.1.1 Ongoing Studies

There are currently no nonclinical pharmacology studies ongoing.

3.1.2 Completed Studies

There were no nonclinical pharmacology studies conducted with X-22 Smoking Cessation Product during this reporting period.

3.2 Pharmacokinetics/Absorption, Distribution, Metabolism, and Excretion

3.2.1 Ongoing Studies

There are currently no nonclinical pharmacokinetic/absorption, distribution, metabolism, and excretion (ADME) studies ongoing.

3.2.2 Completed Studies

There were no nonclinical pharmacokinetic/ADME studies conducted with X-22 Smoking Cessation Product during this reporting period.

3.3 Toxicology

3.3.1 Ongoing Studies

There are currently no toxicology studies ongoing.

3.3.2 Completed Studies

There were no toxicology studies conducted with X-22 Smoking Cessation Product during this reporting period.

4 CHEMISTRY, MANUFACTURING, AND CONTROLS

Yields of "tar", nicotine, carbon monoxide and 2 additional smoke constituents, benzo(a)pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), were measured by Arista Laboratories, Inc. The average levels of the stability constituents monitored are summarized in Table 5. Details of the testing results are provided in Appendices 1, 2, and 3 of this report.

Yields of smoke constituents from the X-22 and the Active Control cigarettes remained stable over time, and the values for X-22 Smoking Cessation Product were within the product specifications.

Table 5 Levels of Stability Constituents in X-22 and Active Control Cigarettes

Average Yields of Stability Constituents Mean (SD)				
"Tar," Nicotine and Carbon Monoxide Yields				
		5/25/2011	9/19/2011	10/7/2011
X-22	"Tar," mg/cig	6.91 (0.26)	6.59 (0.35)	7.33 (0.42)
	Nicotine, mg/cig	0.026 (0.001)	0.026 (0.001)	0.027 (0.002)
	CO, mg/cig	13.1 (0.6)	12.0 (1.3)	12.3 (0.7)
Active Control	Tar, mg/cig	8.71 (0.41)	8.08 (0.34)	8.32 (0.29)
	Nicotine, mg/cig	0.709 (0.039)	0.725 (0.039)	0.678 (0.026)
	CO, mg/cig	11.8 (0.5)	11.6 (0.4)	10.7 (0.6)
Additional Smoke Constituents				
		6/24/2011	9/20/2011	10/7/2011
X-22	Benzo(a)pyrene, ng/cig	3.38 (0.08)	3.15 (0.16)	2.91 (0.11)
	NNK, ng/cig	15.4 (1.1)	13.7 (1.6)	12.4 (1.4)
	NNN, ng/cig	64.2 (2.0)	56.9 (1.75)	57.4 (3.74)
	NAT, ng/cig	6.98 (1.02)	6.40 (0.27)	6.42 (0.43)
	NAB, ng/cig	1.46 (0.31)	1.38 (0.12)	1.64 (0.24)
Active Control	Benzo(a)pyrene, ng/cig	6.97 (0.28)	6.82 (0.60)	6.04 (0.30)
	NNK, ng/cig	59.3 (4.0)	42.3 (3.4)	49.6 (3.6)
	NNN, ng/cig	67.7 (2.66)	45.5 (6.44)	54.22 (3.55)
	NAT, ng/cig	85.6 (1.19)	57.5 (9.34)	73.32 (2.74)
	NAB, ng/cig	10.4 (0.61)	8.42 (1.36)	9.70 (0.54)
Oven Volatiles				
X-22		11.5%	ND	8.6%
Active Control		12.5%	ND	8.3%

Abbreviations: cig = cigarette; NAB = N-nitrosoanabasine; NAT = N-nitrosoanatabine; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = N'-nitrosonornicotine

5 GENERAL INVESTIGATIONAL PLAN

5.1 Broad Objectives for X-22 Smoking Cessation Product Development

The goal of the ongoing Phase II development program will be to evaluate the safety and efficacy profile of X-22 Smoking Cessation Product, the pharmacokinetics of nicotine in the X-22 cigarette, and to determine the optimum dosing regimen in order to design the pivotal Phase III clinical trials for the desired indication.

We will consider studies to evaluate the single and multiple dose pharmacokinetics of nicotine in the X-22 cigarette and the relative bioavailability of nicotine from X-22 cigarettes compared to other sources of NRT, prior to the commencement of Phase III studies. Effects of nicotine concentration in the filler on intake and smoking behavior will be evaluated in Phase IIb and/or Phase III studies.

Phase III studies will be conducted to further evaluate the safety and efficacy of X-22 cigarettes as an aid to smoking cessation.

5.2 Clinical Studies Planned for the Coming Year

22nd Century plans to initiate 2 clinical studies in the coming year. One will be an open-label, randomized, crossover design study to evaluate the pharmacokinetics of nicotine obtained from X-22 Smoking Cessation Product in healthy smokers. Next, 22nd Century plans to start the first Phase III study of X-22 Smoking Cessation Product.

6 INVESTIGATOR BROCHURE

No changes were made to the Investigator’s Brochure during this reporting period. The Investigator's brochure will be updated prior to initiation of the next clinical trial.

7 PHASE 1 PROTOCOL MODIFICATIONS

No amendments to a phase 1 study were made during this reporting period.

8 FOREIGN MARKETING DEVELOPMENTS

No foreign marketing applications for X-22 Smoking Cessation Product have been made or withdrawn nor has X-22 Smoking Cessation Product been suspended from marketing in any foreign country.

9 OUTSTANDING BUSINESS WITH RESPECT TO IND 103,589

There is no outstanding business related to IND 103,589.

10 REFERENCES

NCT01050569. Innovative Interventions for Smoking Cessation. http://clinicaltrials.gov/ct2/show/NCT01050569?term=nct01050569&rank=1

NCT01250301. De-nicotinised Cigarettes Study (Denic). http://clinicaltrials.gov/ct2/show/NCT01250301?term=NCT01250301&rank=1

Walker N, Howe C, Bullen C, Grigg M, Glover M, McRobbie H, Laugesen M, Parag V, Whittaker R. The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial. *Addiction*. 2012;107(10):1857-1867.

11 APPENDICES

Appendix 1
Arista Report # 11131

Appendix 2
Arista Report # 11137

Appendix 3
Arista Report # 11253

Innovative Interventions for Smoking Cessation

The recruitment status of this study is unknown because the information has not been verified recently.

Verified January 2010 by National Institute on Drug Abuse (NIDA).
Recruitment status was Recruiting

Sponsor:
University of Minnesota - Clinical and Translational Science Institute

Collaborator:
National Institute on Drug Abuse (NIDA)

Information provided by:
National Institute on Drug Abuse (NIDA)

ClinicalTrials.gov Identifier:
NCT01050569

First received: January 14, 2010
Last updated: NA
Last verified: January 2010
History: No changes posted

Purpose

The purpose of this study is to evaluate the effect of a combination of the 21 mg nicotine patch and nicotine-free cigarette compared to 21 mg nicotine patch only and nicotine-free cigarette only on abstinence and withdrawal symptoms. The study will determine if adding nicotine replacement medication to the nicotine-free cigarettes will augment treatment compared to nicotine patch only or to nicotine-free cigarettes only.

Condition	Intervention	Phase
Nicotine Addiction	Drug: Nicotine Patch Other: Nicotine Free Cigarettes Other: Nicotine Free Cigarette Plus Nicotine Patch	Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Factorial Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Innovative Interventions for Smoking Cessation: Comparison of Nicotine-free Cigarettes Plus Nicotine Patch; Nicotine-free Cigarettes Alone or Nicotine Patch Alone

Resource links provided by NLM:

MedlinePlus related topics: Quitting Smoking Smoking

Drug Information available for: Nicotine polacrilex

U.S. FDA Resources

Further study details as provided by National Institute on Drug Abuse (NIDA):

Primary Outcome Measures:

- End of treatment abstinence rate [Time Frame: 6 week] [Designated as safety issue: No]
- End of follow-up abstinence rates [Time Frame: 26 weeks] [Designated as safety issue: No]

Secondary Outcome Measures:

- Time to lapse or relapse to tobacco use [Time Frame: 26 weeks] [Designated as safety issue: No]
- Effect on nicotine withdrawal [Time Frame: 8 weeks] [Designated as safety issue: Yes]
- Exposure to tobacco toxicants [Time Frame: 6 weeks] [Designated as safety issue: Yes]
- Exploratory predictors of cessation and relapse [Time Frame: 26 weeks] [Designated as safety issue: No]

Estimated Enrollment: 219
Study Start Date: October 2008
Estimated Study Completion Date: May 2011
Estimated Primary Completion Date: March 2011 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Active Comparator: Nicotine Free Cigarette Nicotine Free Cigarette	Other: Nicotine Free Cigarettes Cigarette where the tobacco contains 0.05 mg of nicotine or less. Other Name: Quest 3
Active Comparator: Nicotine Patch 21 mg nicotine patch	Drug: Nicotine Patch 21 mg Other Name: Nicoderm CQ
Experimental: Nicotine Free Cigarette plus Nicotine Patch Nicotine Free Cigarette plus Nicotine Patch	Other: Nicotine Free Cigarette Plus Nicotine Patch 21 mg nicotine patch plus use of cigarette with tobacco containing 0.05 mg nicotine. Other Names: • Nicoderm CQ • Quest 3

Detailed Description:
The purpose of this study is to evaluate the effect of a combination of the 21 mg nicotine patch and nicotine-free cigarette compared to the nicotine-free cigarette alone or 21 mg nicotine patch alone on abstinence and withdrawal.

The following primary hypothesis will be tested:

-1)Abstinence rates will be highest and the time to relapse will be the longest in the nicotine-free cigarettes plus nicotine patch condition compared to nicotine patch or nicotine-free cigarettes alone.

Other hypotheses include:

- 1)Greater positive subjective responses to cigarettes will be observed with nicotine-free cigarettes plus patch vs. nicotine-free cigarette;
- 2)Less drop-outs will be observed in the nicotine-free plus patch vs the other two conditions;
- 3)Similar withdrawal symptoms and negative affect will be observed with nicotine-free cigarette condition and the nicotine patch alone condition, and least withdrawal and negative affect with the nicotine-free cigarette plus nicotine patch condition; and
- 4)Less compensatory smoking will be observed in the nicotine-free plus patch condition compared to nicotine-free cigarette alone condition.

Cigarette smokers will be randomized to:

1)denicotinized cigarettes (which provide sensory behavioral aspects of smoking but with no nicotine) plus nicotine patch for 6 weeks; -2)nicotine patch for 6 weeks; or - 3)denicotinized cigarettes alone.

Outcome measures will include cessation assessed at the end of treatment as the primary endpoint and at 12, 16, 24 and 36 weeks post-treatment, time to lapse and relapse to usual brand cigarettes, withdrawal symptoms and craving and biomarkers of toxicant exposure. Predictors of abstinence and treatment response for each of the treatment conditions will be explored.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: Yes

Criteria
Inclusion Criteria:

- a) Smoking at least 10 cigarettes daily for the past year;
- b) In good physical health;
- c) No contraindications for medicinal nicotine; and
- d) Stable, good mental health.

Exclusion Criteria:

- a) Subjects must not be using other tobacco or nicotine products.
- b) Female subjects cannot be pregnant or nursing and must be using appropriate birth control.

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01050569

Contacts

Contact: Joni Jensen, MPH 612-624-5178 jense010@umn.edu

Contact: Louise Hertsgaard, MA 612-624-4913 hert0002@umn.edu

Locations

United States, Minnesota

University of MN's Tobacco Use Research Center **Recruiting**
Minneapolis, Minnesota, United States, 55414
Contact: Joni Jensen, MPH 612-624-5178 jense010@umn.edu
Principal Investigator: Dorothy **Hatsukami**, PhD

Sponsors and Collaborators

University of Minnesota - Clinical and Translational Science Institute

National Institute on Drug Abuse (NIDA)

Investigators

Principal Investigator: Dorothy **Hatsukami**, PhD University of Minnesota - Clinical and Translational Science Institute

More Information

No publications provided

Responsible Party:	Dorothy Hatsukami, Ph.D., University of Minnesota
ClinicalTrials.gov Identifier:	NCT01050569 History of Changes
Other Study ID Numbers:	1R01DA025598, R01DA025598, DPMC
Study First Received:	January 14, 2010
Last Updated:	January 14, 2010
Health Authority:	United States: Federal Government

Keywords provided by National Institute on Drug Abuse (NIDA):
Smoking Cessation
Nicotine Free Cigarettes

Additional relevant MeSH terms:

Tobacco Use Disorder
Smoking
Behavior, Addictive
Substance-Related Disorders
Mental Disorders
Habits
Compulsive Behavior
Impulsive Behavior
Nicotine
Nicotine polacrilex
Ganglionic Stimulants
Autonomic Agents
Peripheral Nervous System Agents
Physiological Effects of Drugs
Pharmacologic Actions
Nicotinic Agonists
Cholinergic Agonists
Cholinergic Agents
Neurotransmitter Agents
Molecular Mechanisms of Pharmacological Action
Central Nervous System Stimulants
Central Nervous System Agents
Therapeutic Uses

ClinicalTrials.gov processed this record on September 20, 2012

De-nicotinised Cigarettes Study (Denic)

This study has been completed.

Sponsor:
Queen Mary University of London

Collaborator:
Pfizer

Information provided by (Responsible Party):
Hayden McRobbie, Queen Mary University of London

ClinicalTrials.gov Identifier:
NCT01250301

First received: November 29, 2010
Last updated: July 16, 2012
Last verified: July 2012
History of Changes

Purpose

The aim of this study is to determine if using a behavioural replacement for smoking (de-nicotinised cigarettes; DNCs), in addition to standard treatment during the first two weeks after the target quit date, can reduce urges to smoke over the first 4-weeks of abstinence. Two hundred smokers who want to quit will be recruited from the community. They would all receive standard smoking cessation treatment from the NHS Stop Smoking Service (NHS SSS), which uses a combination of stop smoking medication (e.g. nicotine replacement therapy, Champix) and motivational support. On their target quit date, participants would be randomised to receive behavioural replacement (i.e. use of de-nicotinised cigarettes) plus standard treatment for the first two weeks of their quit attempt, or to continue with standard treatment alone. De-nicotinised cigarettes are similar to standard cigarettes except that they do not deliver nicotine to the smoker. Participants will rate their urges to smoke at each week. Standard NHS SSS measures will also be taken in addition to user acceptability ratings and reactions to smoking cues.

The hypothesis is that complementing current NHS SSS treatments with de-nicotinised cigarettes, to address the non-nicotine factors associated with smoking and to help extinguish smoking behaviour, would result in lower urges to smoke than standard treatment alone.

Condition	Intervention
Smoking Cessation Tobacco Dependence	Other: De-nicotinised cigarettes + standard treatment Other: Standard Treatment

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Complementing Current NHS Stop Smoking Service Treatments for Smokers With Behavioural Replacement: The Role of De-nicotinised Cigarettes

Resource links provided by NLM:

MedlinePlus related topics: Quitting Smoking Smoking

U.S. FDA Resources

Further study details as provided by Queen Mary University of London:

Primary Outcome Measures:

- Urges to smoke in first week of abstinence [Time Frame: 1 week] [Designated as safety issue: No]

Differences in urges to smoke in the first week of abstinence between participants who receive a behavioural replacement (DNCs) plus standard NHS SSS treatment, with those who receive standard NHS SSS treatment alone, will be measured by the Mood and Physical Symptoms Scale (MPSS; West & Hajek, 2004).

Secondary Outcome Measures:

- Change in ratings of tobacco withdrawal symptoms, measured by the MPSS [Time Frame: First 4 weeks of abstinence (from baseline- 4 weeks post-quit)] [Designated as safety issue: No]
- CO-validated continuous abstinence rates [Time Frame: 4-weeks] [Designated as safety issue: No]

  CO-validated continuous abstinence rates will be measured 1-4 weeks following the target quit day in the standard treatment condition and 1-4 weeks following cessation of DNCs in the DNC condition.

- Acceptability and user reactions to DNCs [Time Frame: 2 weeks] [Designated as safety issue: No]
- Urges to smoke 24 hours after quitting, measured by the MPSS [Time Frame: 24 hours] [Designated as safety issue: No]
- Profile of adverse effects up to 12 weeks post quitting [Time Frame: 12 weeks] [Designated as safety issue: Yes]
- Reactions to smoking cues [Time Frame: 12 weeks] [Designated as safety issue: No]

  The differences in reactions to smoking cues between the 2 groups will be measured with smoking-related images and by the Cue Exposure Subscale of the Wisconsin Inventory for Smoking Dependence (WISDM-68; Piper, et al., 2004).

Enrollment: 200
Study Start Date: July 2011
Study Completion Date: July 2012
Primary Completion Date: April 2012 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: De-nicotinised cigarettes + standard treatment	Other: De-nicotinised cigarettes + standard treatment Participants will receive de-nicotinised cigarettes to use as required for 2 weeks after their quit day. These cigarettes are intended to provide a replacement for the behavioural and sensory aspects of smoking without supplying nicotine. Participants will also receive standard NHS Stop Smoking Service treatment. This is a combination of weekly behavioural support and medication (e.g. nicotine replacement therapy/varenicline). Other Names: • NHS Stop Smoking Service • De-nicotinised cigarettes
Active Comparator: Standard treatment	Other: Standard Treatment Participants will receive standard treatment from the NHS Stop Smoking Service.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: Yes

Criteria
Inclusion Criteria:

- 18 years or over
- Seeking treatment to stop smoking

Exclusion Criteria:

- Pregnant or breastfeeding
- Acute psychiatric illness

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01250301

Locations

United Kingdom

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London, United Kingdom, E1 2JH

Sponsors and Collaborators

Queen Mary University of London

Pfizer

Investigators

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More Information

No publications provided

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The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial

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ABSTRACT

Aim To determine the combined effect of very low nicotine content (VLNC) cigarettes and usual Quitline care [nicotine replacement therapy (NRT) and behavioural support] on smoking abstinence, in smokers motivated to quit. **Design** Single-blind, parallel randomized trial. **Setting** New Zealand. **Participants** Smokers who called the Quitline for quitting support were randomized to either VLNC cigarettes to use whenever they had an urge to smoke for up to 6 weeks after their quit date, in combination with usual Quitline care (8 weeks of NRT patches and/or gum or lozenges, plus behavioural support) or to usual Quitline care alone. **Measurements** The primary outcome was 7-day point-prevalence smoking abstinence 6 months after quit day. Secondary outcomes included continuous abstinence, cigarette consumption, withdrawal, self-efficacy, alcohol use, serious adverse events and views on the use of the VLNC cigarettes at 3 and 6 weeks and 3 and 6 months. **Findings** A total of 1410 participants were randomized (705 in each arm), with a 24% loss to follow-up at 6 months. Participants in the intervention group were more likely to have quit smoking at 6 months compared to the usual care group [7-day point-prevalence abstinence 33 versus 28%, relative risk (RR) = 1.18, 95% confidence interval (CI): 1.01, 1.39, $P = 0.037$; continuous abstinence 23 versus 15%, RR = 1.50, 95% CI: 1.20, 1.87, $P = 0.0003$]. The median time to relapse in the intervention group was 2 months compared to 2 weeks in the usual care group ($P < 0.0001$). **Conclusions** Addition of very low nicotine content cigarettes to standard Quitline smoking cessation support may help some smokers to become abstinent.

Keywords Cessation, clinical trial, nicotine replacement therapy, Quest 3, randomized, reduced nicotine cigarettes, smoking.

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INTRODUCTION

Smoking cessation treatments are part of a comprehensive package of strategies aimed at helping people to quit. However, most people who achieve short-term abstinence relapse within a year. Current cessation strategies tend to focus on alleviating nicotine withdrawal symptoms and craving or helping people to cope with such symptoms. Although pharmacological treatments such as nicotine replacement therapy (NRT), bupropion and varenicline are of proven effectiveness, none address the non-nicotine aspects of tobacco smoking, such as the tactile action of puffing on a cigarette, the sensation of smoke in the mouth and throat [1], the smell and taste and the

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activity of other psychoactive substances in tobacco smoke that may strengthen nicotine dependence (such as acetaldehyde [2] or monoamine oxidase inhibitors [3]).

Reduced nicotine cigarettes (RNCs) offer the closest replacement to regular cigarettes. A number of different RNC brands have been marketed by tobacco companies, but the majority of research has been undertaken using the 'Quest' brand, produced and marketed by Vector Tobacco, Inc. (Miami, FL, USA). Three 'strengths' (1, 2 and 3) of Quest RNCs were produced with nicotine yields of 0.6 mg, 0.3 mg and ≤0.05 mg per cigarette, respectively, a nicotine content of 8.9 mg, 5.1 mg and 0.5 mg per cigarette, respectively, and a tar content of between 8 and 9 mg per cigarette (similar to the level in regular cigarettes) [4]. Quest RNCs were marketed to smokers as a way of reducing their nicotine consumption over time, but never as a way of achieving complete abstinence, despite evidence from five small trials (n = 35–346) [4–7] that suggested the use of RNCs alone [7,8] or in combination with NRT [4–6] may help smokers to address both the nicotine and non-nicotine aspects of smoking, with a positive impact on withdrawal, craving and quitting success [9]. Based on this evidence [9], we designed a large, community-based, parallel group, randomized controlled trial to determine the combined effect of using RNCs and usual Quitline care (NRT and behaviour support) on long-term quit rates in smokers motivated to quit. We selected the lowest nicotine-content cigarettes (Quest 3) to minimize the issue of compensatory smoking [4], and refer to these cigarettes hereafter as very low nicotine content (VLNC) cigarettes. We hypothesized that quit rates would be increased by offering smokers who wanted to quit VLNC cigarettes together with usual Quitline care.

METHODS

Setting and participants

The rationale and methodology for this trial have been reported previously [10]. Between April 2009 and October 2010 all eligible callers to New Zealand's Quitline were invited to participate. Participants were eligible if they were aged ≥18 years, smoked their first cigarette within 30 minutes of waking, were interested in trying to quit smoking now, were not pregnant/breastfeeding, were not currently using NRT or non-cigarette tobacco products, had not experienced a stroke or angina in the last 2 weeks, were not using bupropion, clonidine, nortriptyline or varenicline, were not enrolled in alternative Quitline support programmes and could provide verbal consent. Ethics approval for the trial was obtained from the NZ Multi-region Ethics Committee (MEC/08/10/117). The trial is registered with the Australasian Clinical Trials Network: ACTRN12608000410358.

Randomization, allocation concealment and blinding

Participants were allocated randomly in a 1 : 1 ratio by computer, with stratified minimization by sex, ethnicity [Māori (the indigenous people of New Zealand) versus non-Māori] and level of nicotine dependence (>5 points or ≤5 points on the Fagerström Test of Nicotine Dependence [11]). Participants were not blinded to treatment allocation, but research staff undertaking outcome assessment were blinded.

Intervention

Participants were randomized to VLNC cigarettes plus usual Quitline care (NRT and behavioural support) or usual Quitline care alone.

Intervention group participants were delivered a carton of 200 VLNC cigarettes (Quest 3 brand; Vector Tobacco Inc.) by courier, at no cost. Participants were instructed to stop smoking their regular cigarettes on their designated quit day (QD) and to smoke the VLNC cigarettes *ad libitum* whenever they had an urge to smoke during the subsequent 6 weeks. In addition, participants received standard smoking cessation support through Quitline (as described below). No additional instructions were given about the combined use of the VLNC cigarettes and NRT, and no restrictions were placed on the number of VLNC cigarettes smoked per day. Participants could request a second carton of the cigarettes at a 3-week follow-up call. Independent verification of nicotine and tar content by Labstat Canada found the VLNC cigarettes had a nicotine content of 1.5 mg per cigarette, a nicotine yield of ≤0.05 mg per cigarette and a tar content of 4 mg per cigarette (not 8–9 mg as in previously tested Quest 3 cigarettes). The cigarettes used in the trial were not available for general sale in New Zealand.

Participants randomized to the usual Quitline care group received an 8-week supply of NRT (7, 14 or 21 mg patch, and/or 2 or 4 mg gum or 2 mg lozenge) issued by post via a voucher. Participants were instructed to redeem the voucher at a pharmacist for subsidized NRT (NZ$3 per item per 4 weeks' supply, equivalent to approximately €2 or US$2.5). The strength and type of NRT was determined by the Quitline adviser, based on each person's level of nicotine dependency and Quitline guidelines. Usual Quitline care also included an average of three behavioural support calls from trained Quitline advisers over 8 weeks, each call lasting 10–15 minutes. QD in this study referred to the day each participant stopped smoking regular cigarettes (containing nicotine).

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Outcome measures

All data were collected by telephone. Baseline data included socio-demographic characteristics, smoking history and quitting self-efficacy [belief in their ability to quit measured on a scale of 1 (very low) to 5 (very high)]. Tobacco withdrawal symptoms were measured using the Mood and Physical Symptoms Scale (MPSS) [12], with additional questions on disturbed sleep, anxiety, mouth ulcers, cough, impatience, dizziness and increased dreaming [13]. Alcohol use and misuse was measured using the Alcohol Use Disorders Identification Test (AUDIT-C) [14].

Outcome data were collected at 3 and 6 weeks and 3 and 6 months after QD. The primary outcome was self-reported 7-day point-prevalence of smoking abstinence 6 months after QD (defined as no regular cigarettes, not a single puff, in the previous 7 days [15]). Biochemical verification of abstinence was not undertaken. Details on secondary outcomes are reported in another publication [10]; they included continuous abstinence (self-report of smoking not more than five regular cigarettes since QD [15]), use of NRT (type, dose and quantity per day), other cessation treatments used during the study period, concomitant medication and cost-related outcomes. Intervention group participants were also asked at 3 and 6 weeks about the number of VLNC cigarettes smoked per day, whether they would recommend them to friends and family who smoked and wanted to quit, if they had concerns about the use of VLNC cigarettes and the extent to which they experienced any rewarding effects from smoking VLNC cigarettes [assessed using the modified Cigarette Evaluation Questionnaire (mCEQ), which measures smoking satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations and craving reduction [16]]. At 6 weeks participants in the intervention group were also asked if they felt that 6 weeks was a long enough period to use the VLNC cigarettes.

Sample size

The sample size of 1410 people (705 in each group) assumed a quit rate in the usual care group of 15%, loss to follow-up of 20%, and conferred 90% power at $P = 0.05$ to detect a difference in point-prevalence abstinence of 7.5%. A fixed proportion of at least 25% Māori was sought by adjusting the sampling ratio according to self-reported ethnicity [17]. Māori, who comprise 15% of the NZ population, have a high smoking prevalence (46% in 2008 [18]) and appear to metabolize nicotine more slowly than non-Māori [19,20]. This recruitment strategy for Māori ensures that they are not underrepresented in research of relevance to them [21,22].

Analyses

Analyses were undertaken on an intention-to-treat basis, and per-protocol analysis was performed to check for robustness of results. Participants with missing smoking status data, withdrawals or lost to follow-up were considered to be still smoking [15]. We used χ^2 analysis to compare the proportion quit by treatment group. Pre-specified subgroup analyses were undertaken for ethnicity (Māori, non-Māori), age (<40 years, ≥40 years), sex and socio-economic status (dichotomized as those who left school below year 12 or with no school qualification, and those who completed year 12 and above). Repeated-measures analyses were also undertaken using generalized estimating equation (GEE) models to assess the treatment effect over time, and to mitigate the effect of missing data (when missing at random). The analyses included an interaction between treatment group and time, and adjustment for gender, ethnicity and nicotine dependence. Change in number of cigarettes per day and withdrawal symptoms (in abstainers only) over time were analysed using repeated-measures mixed models and adjusted for baseline value. Time-to-first-lapse was analysed by Kaplan–Meier analysis. Serious adverse events were defined as per the International Conference on Harmonisation Guideline for Clinical Safety Data Management [23], and coded using ICD-10AM. Three *post-hoc* analyses were undertaken to assess the heterogeneity of the primary outcome according to type of cigarettes smoked (factory-made only, roll-your-own only or both), baseline alcohol use (AUDIT-C: female: <3, ≥3, and male: <4, ≥4) and if at least one quit attempt or not had been made in the last 12 months.

RESULTS

Figure 1 shows participant flow throughout the trial and Table 1 shows participant baseline characteristics. Final loss to follow-up for the trial was 24%. The number of requested withdrawals from the trial was significantly higher in the usual care group compared with the intervention group (32 people versus 11 at 6 months, $P = 0.001$). No difference was seen in baseline variables between those in the usual care group who withdrew compared to those who did not withdraw.

Cessation rates

Seven-day point-prevalence 6-month abstinence rates were significantly greater in the intervention group (231, 33%) compared to the usual care group (195, 28%) [crude relative risk (RR) 1.18, 95% confidence interval (CI): 1.01, 1.39, $P = 0.037$; absolute risk difference 0.051, 95% CI: 0.003, 0.099; number needed to treat

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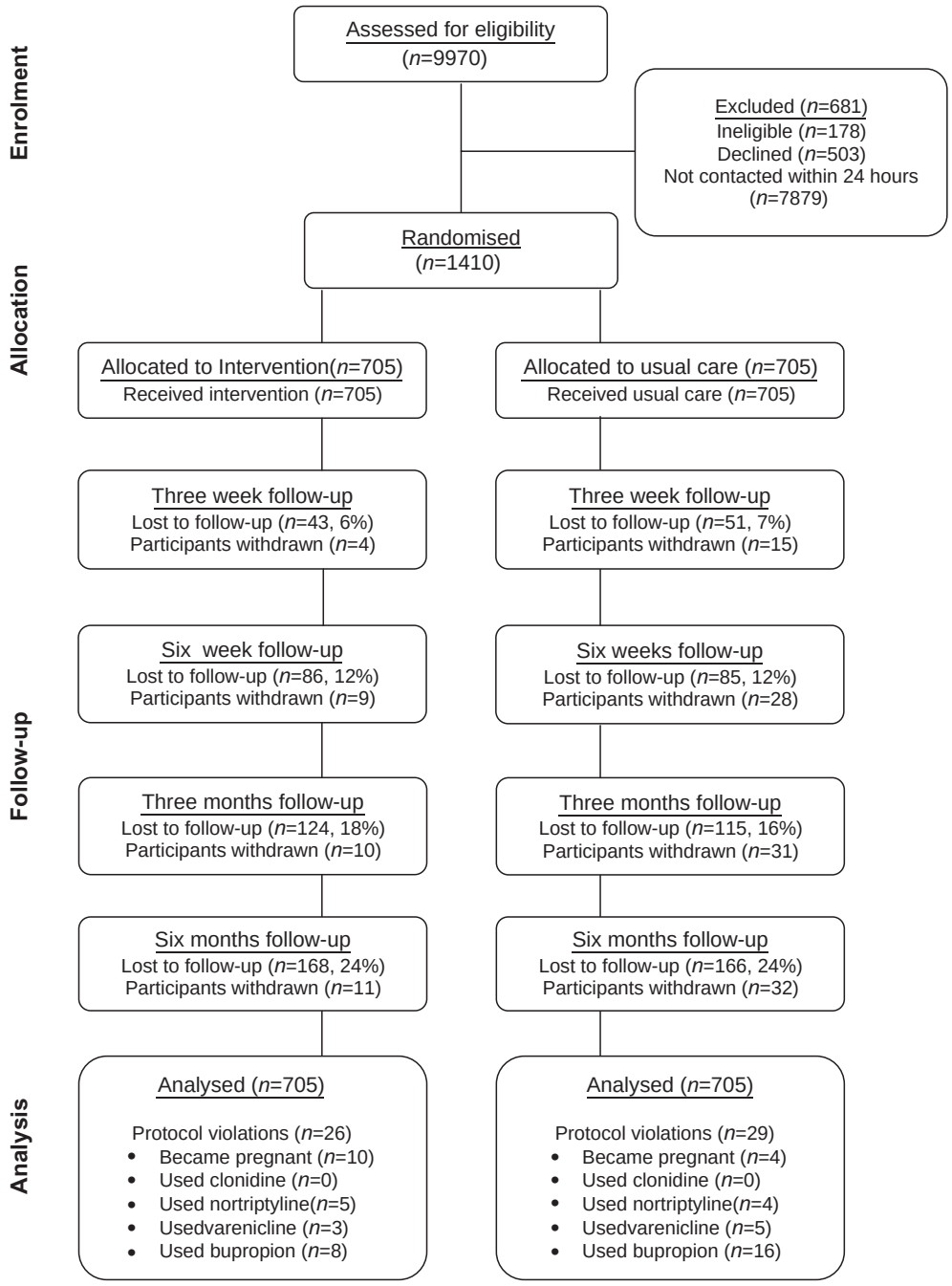


Figure 1 Flow-chart of recruitment and retention of participants throughout the trial

(NNT) = 19.6] (Table 2). Results were similar when only participants with complete smoking data were included and with per protocol analyses. Subgroup analyses showed no difference in the primary outcome according to age, sex, ethnicity, socio-economic status, type of cigarettes smoked, alcohol use at baseline, level of nicotine dependence or whether at least one quit attempt had been made in the last 12 months. Use of GEE repeated-measures analysis showed a highly significant time and treatment effect, with the treatment effect strongest earlier in the intervention period (Table 2).

Using continuous abstinence as the measure of outcome showed that 160 (23%) participants from the intervention group and 107 (15%) in the usual care group were abstinent at 6 months. This result gave a crude RR of 1.50 (95% CI: 1.20, 1.87) with a *P*-value of 0.0003, an absolute risk difference of 0.08 (95% CI: 0.03, 0.12) and NNT of 13 (Table 2).

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Table 1 Baseline characteristics of participants.

Variables	*Intervention group n = 705 (%)*	*Usual care group n = 705 (%)*
Sex		
Female	413 (59)	413 (59)
Male	292 (41)	292 (41)
Age (years)		
Mean	41.1	42.4
SD	12.4	12.7
Ethnicity		
Māori	171 (24)	170 (24)
Non-Māori	534 (76)	535 (76)
Education		
Below year 12/no qualification	363 (51)	371 (53)
Year 12 and above	342 (49)	330 (47)
Refused to answer	0	4
Cigarettes smoked per day		
Mean	21.8	21.4
SD	9.8	9.4
Fagerström Test of Nicotine Dependence (1–10)[a]		
Mean	6.2	6.2
SD	1.7	1.7
Type of cigarettes smoked		
Factory-made only	263 (37)	301 (43)
Roll-your-own only	375 (53)	346 (49)
Both	67 (10)	58 (8)
'Roll-your-own' smokers		
Grams smoked per week (mean, SD)	52.2 (23.9)	54.0 (27.2)
Pouch size in grams (mean, SD)	39.5 (9.9)	39.4 (9.9)
Days taken to smoke contents (mean, SD)	5.9 (2.2)	5.8 (1.9)
Lives with other smokers		
Yes	342 (49)	324 (46)
No	363 (52)	377 (54)
Missing	0	4 (1)
At least one quit attempt in last 12 months	217 (31)	198 (28)
Last method used to quit		
NRT patch	37 (17)	32 (16)
NRT gum	10 (5)	8 (4)
NRT lozenge	0	4 (2)
Zyban	2 (1)	3 (2)
Other	17 (8)	15 (8)
Nothing	151 (70)	136 (69)
Alcohol use (AUDIT-C: 0–12)[b]		
Female (mean, SD)	4.2 (3.1)	4.1 (3.2)
Male (mean, SD)	5.6 (3.5)	5.5 (3.6)
Self-efficacy[c]		
Mean	4.2	4.2
SD	0.8	0.8

SD: standard deviation; NRT: nicotine replacement therapy; AUDIT: Alcohol Use Disorders Identification Test. [a]A higher level of dependence was noted in Māori ($n = 341$, mean score = 6.4, SD = 1.4) compared to non-Māori ($n = 1069$, mean score = 6.1, SD = 1.7; $P = 0.008$) participants. [b]For men, a score ≥ 4 indicates an increased risk of hazardous drinking or alcohol dependence, while in women it is a score of ≥ 3. The higher the score, the greater the risk of alcohol dependence. [c]Belief in their ability to quit this time, measured on a scale of 1–5, where 1 was 'very low' and 5 was 'very high'.

Time to first lapse

Results of the time-to-first-lapse Kaplan–Meier analysis showed a significant difference between groups in favour of the intervention group, with 391 versus 465 participants relapsing within 6 months [median days to relapse: 61 in the intervention compared to 13 days for the usual care group, *P*-value for log-rank test

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Table 2 Point-prevalence and continuous abstinence rates, by treatment group (intention-to-treat analysis).

	Intervention n = 705 (%)	*Usual care n = 705 (%)*	*Relative risk (95% CI)*	*P-value*
Seven-day point-prevalence abstinence				
Three-week quit rate[a]	378 (54)	256 (36)	1.48 (1.31–1.66)	<0.0001
Six-week quit rate[a]	333 (47)	232 (33)	1.44 (1.26–1.64)	<0.0001
Three-month quit rate[a]	280 (40)	211 (30)	1.33 (1.15–1.53)	0.0001
Six-month quit rate (primary outcome)[a]	231 (33)	195 (28)	1.18 (1.01–1.39)	0.037
Sensitivity analyses for 6-month quit data				
Complete cases only[b]	231/537 (43)	195/539 (36)	1.19 (1.03–1.38)	0.022
Per protocol[c]	224/512 (44)	186/513 (36)	1.21 (1.04–1.40)	0.014
Repeated-measures analyses[d]				
Overall treatment effect	–	–	1.67 (1.39–2.00)	<0.0001
Three-week effect	–	–	2.06 (1.66–2.56)	<0.0001
Six-week effect	–	–	1.86 (1.49–2.31)	<0.0001
Three-month effect	–	–	1.56 (1.25–1.95)	<0.0001
Six-month effect			1.29 (1.02–1.62)	0.03
Continuous abstinence				
Three-week quit rate[a]	393 (56)	275 (39)	1.43 (1.28–1.60)	<0.0001
Six-week quit rate[a]	293 (42)	203 (29)	1.44 (1.25–1.67)	<0.0001
Three-month quit rate[a]	227 (32)	148 (21)	1.53 (1.28–1.83)	<0.0001
Six-month quit rate[a]	160 (23)	107 (15)	1.50 (1.20–1.87)	0.0003

Six-month 7-day point-prevalence abstinence is the primary outcome. All other variables presented are secondary outcomes. CI: confidence interval. [a]Assumes all participants with missing smoking status were smoking (including those who withdrew). [b]Only includes participants for whom data on smoking status was complete at 6 months (withdrawn participants excluded). [c]Excludes participants with missing 6-month data and protocol violations. [d]Adjusted for gender, ethnicity and level of nicotine dependence.

<0.0001, hazard ratio (HR) = 0.70, 95% CI: 0.61, 0.80] (Fig. 2).

Use of the VLNC cigarettes

Overall, 94% (583) of the 619 participants in the intervention group who could be contacted at 6 weeks had smoked the VLNC cigarettes given to them, with 21% ($n = 132$) asking for a second carton. The average number of VLNC cigarettes smoked weekly decreased during the 6-week intervention period (Table 3). Table 3 also summarizes whether participants smoked the VLNC cigarettes with or without the use of NRT and/or whether or not they also smoked their regular cigarettes.

At 6 weeks, 90% (560) of the remaining 619 participants in the intervention arm said they would recommend the VLNC cigarettes to friends and family who smoked and wanted to quit. The main reasons given by the 10% of participants not recommending the cigarettes were: they would encourage them to start smoking 'normal cigarettes' again (29%); the cigarettes were habit-forming (19%); and they gave no relief from cravings (17%). In addition, 11% (65) of the 619 had concerns about using the VLNC cigarettes—these were that the cigarettes were still bad for your health (31%); that they would encourage them to start smoking 'normal cigarettes' again (12%); and the cigarettes were habit-forming (6%). Seventy per cent (435) felt that 6 weeks was a long enough period to use the cigarettes, with 19% (119) preferring a longer period (mean suggested period: 76 days, SD = 45 days, median 90 days), 2% (12) a shorter period (mean suggested period: 24 days, SD = 22 days, median 18 days) and 9% (53) unsure.

The mean mCEQ subscale scores for participants in the intervention group (302 answered the mCEQ at both 3 and 6 weeks) were not statistically different between weeks 3 and 6, or according to NRT use or non-use. Participants reported 'a little' to a 'moderate' level of smoking satisfaction and psychological reward from using the VLNC cigarettes (Table 4). There was 'very little' to 'a little' aversion and enjoyment of the respiratory tract sensations associated with use of the VLNC cigarettes, but craving reduction was 'moderate' to 'a lot' (Table 4).

Other outcomes

There was no significant difference between the intervention group and the usual care group in the average amount of NRT used in abstainers at any time point (Table 5) or in the proportion of participants who had reduced their daily consumption of regular cigarettes by at least 25% at 6 months ($n = 467$, 66% intervention versus $n = 445$, 63% usual care, RR = 1.05, 95% CI: 0.97, 1·13, $P = 0.2$). For abstainers only, symptoms associated with nicotine withdrawal and urges to smoke did

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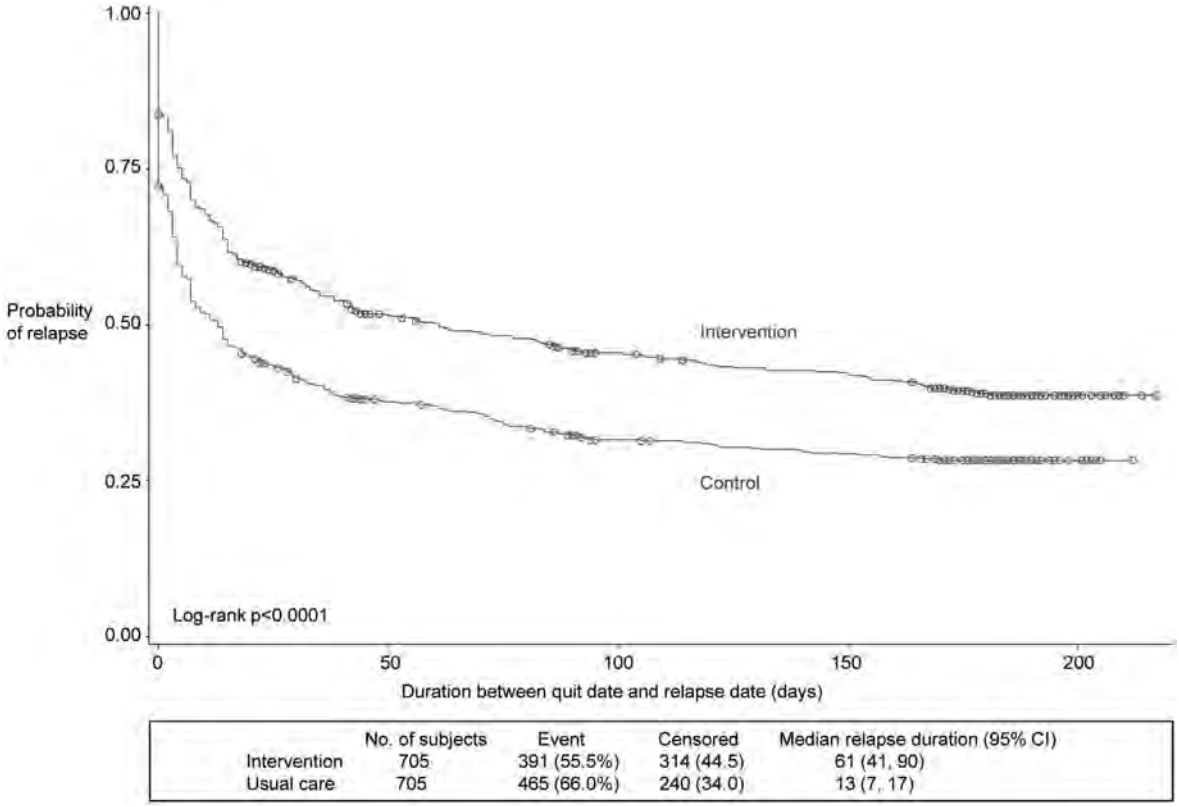


Figure 2 Kaplan–Meier curve for time to first relapse (days)

Table 3 Very low nicotine content (VLNC) cigarettes smoked, during the 6-week intervention period.

Number of VLNC cigarettes smoked each week

	Mean (SD)	*Median, range*
Week 1 ($n = 662$)	26 (31)	20, 0–200
Week 2 ($n = 662$)	20 (26)	10, 0–120
Week 3 ($n = 662$)	13 (21)	3, 0–140
Week 4 ($n = 619$)	10 (19)	0, 0–200
Week 5 ($n = 618$)	8 (16)	0, 0–100
Week 6 ($n = 618$)	6 (13)	0, 0–80

Use of the VLNC cigarettes, with NRT and regular cigarettes

	Intervention n = 619 (%)	*Usual care n = 617 (%)*
Smoked VLNC cigarettes and regular cigarettes, and used NRT	235 (38%)	–
Smoked VLNC cigarettes and used NRT	149 (24%)	–
Smoked VLNC cigarettes and regular cigarettes	135 (22%)	–
Smoked VLNC cigarettes only	64 (10%)	–
Used NRT only	13 (2%)	106 (17%)
Smoked regular cigarettes only	13 (2%)	187 (30%)
Used nothing	8 (1%)	33 (5%)
Smoked regular cigarettes and used NRT	2 (0.3%)	291 (47%)

SD: standard deviation; NRT: nicotine replacement therapy. No definition of 'smoked VLNC cigarettes' was provided, thus users may have had only a few puffs or more than one cigarette. 'Smoked regular cigarettes' was defined as having smoked more than one nicotine-containing cigarette. No ethnic differences in the data were observed.

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Table 4 Views on the use of the very low nicotine content (VLNC) cigarettes, as measured using the modified cigarette evaluation questionnaire (intervention group only).

	Three weeks	*Six weeks*
	Mean (SD) (n = 302)[a]	*Mean (SD) (n = 302)*[a]
Smoking satisfaction		
Did you find the cigarettes satisfying?	3.8 (2.0)	3.9 (2.1)
Did the cigarettes taste good?	2.9 (1.9)	3.1 (1.9)
Did you enjoy smoking the cigarettes?	3.9 (2.2)	3.7 (2.1)
Average score	3.5 (1.7)	3.5 (1.7)
Psychological reward		
Did smoking the cigarettes calm you down?	4.2 (2.0)	4.2 (1.9)
Did smoking the cigarettes make you feel more awake?	2.4 (1.9)	2.5 (1.9)
Did smoking the cigarettes make you feel more irritable?	4.0 (2.0)	3.9 (2.0)
Did smoking the cigarettes help you concentrate?	3.3 (2.1)	3.1 (2.1)
Did smoking the cigarettes reduce your hunger for food?	2.6 (2.0)	2.5 (2.0)
Average score	3.3 (1.5)	3.2 (1.5)
Aversion		
Did smoking the cigarettes make you less dizzy?	2.5 (2.0)	2.5 (2.0)
Did smoking the cigarettes make you nauseous?	1.5 (1.2)	1.5 (1.3)
Average score	2.0 (1.2)	2.0 (1.3)
Enjoyment of respiratory tract sensations		
Did you enjoy the sensation in your throat and chest?	2.9 (2.0)	3.0 (2.0)
Craving reduction		
Did smoking the cigarettes immediately relieve your craving for a cigarette?	4.8 (2.0)	4.7 (2.1)

SD: standard deviation. [a]Those participants in the intervention group who were using the VLNC cigarettes ± nicotine replacement therapy (NRT) during the 6-week study period, and answered the modified Cigarette Evaluation Questionnaire (mCEQ) at both 3 and 6 weeks. Each scale is 1–7, where: 1 is 'not at all', 2 is 'very little', 3 is 'a little', 4 is 'moderately', 5 is 'a lot', 6 is 'quite a lot' and 7 is 'extremely'.

Table 5 Mean amount of nicotine replacement therapy (NRT) used over time in abstainers.

Time-period	*Mean NRT used in mg/day (SD)*	*Median*	*P-value*[a]
Three weeks			
Intervention (*n* = 231)	15.3 (12.2)	21	0.89
Usual care (*n* = 195)	15.6 (12.5)	21	
Six weeks			
Intervention (*n* = 231)	11.7 (11.9)	11	0.87
Usual care (*n* = 195)	11.7 (13.1)	6	
Three months			
Intervention (*n* = 231)	3.2 (7.5)	0	0.15
Usual care (*n* = 195)	4.4 (8.3)	0	
Six months			
Intervention (*n* = 231)	2.1 (5.9)	0	0.83
Usual care (*n* = 195)	1.6 (5.0)	0	

SD: standard deviation. [a]From Wilcoxon's Mann–Whitney *U*-test.

not differ significantly between each group from baseline to 6 weeks. Participants who were abstinent at 6 months were asked about their use of non-NRT methods of cessation during the trial—four participants in the intervention arm had used another pharmaceutical intervention (namely bupropion, nortriptyline or varenicline) compared to nine in the usual care arm. A further 11 participants in the intervention arm compared to nine in the usual care arm had used a non-pharmaceutical cessation intervention; namely, Allan Carr, hypnosis, exercise, alternative medicine, sweets, 'cold turkey', psychological support or nicotine-free e-cigarettes.

There was no significant difference in the occurrence of serious adverse events between the intervention group (36 events in 36 participants, 5·1%) and usual care group (35 events in 35 participants, 5.0%, incidence rate ratio = 1.04, 95% CI: 0.65, 1·65, $P = 0.9$). Injuries to the body (eight versus four events) and mental and behavioural disorders (two versus no events) were more common in the intervention group than the usual care group, while in the usual care group more gastrointestinal events (four versus seven events) and symptoms and signs (one versus six events) occurred. All other events were similar in both groups. There were two deaths, one in each group, both due to cancer.

Data on concomitant medication and cost-related outcomes will be presented in subsequent publications.

DISCUSSION

This is the largest trial conducted to date that explores the combined effect of VLNC cigarettes and usual Quitline care (NRT and behavioural support) on short- and

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long-term abstinence rates in people motivated to quit. A clear increase in quit rates over usual Quitline care was found, with a positive impact on time to relapse and high participant acceptability. In abstainers, NRT use was similar in both groups and very few participants used non-trial cessation interventions during the study period, adding weight to the strong effect of the VLNC cigarettes, particularly within the first 3 weeks of quitting. This finding suggests that VLNC cigarettes may be associated not only with extinction, but may provide a coping mechanism to get through the initial stages of abstinence by replacing some of the conditioned rituals associated with smoking, such as the hand-to-mouth action, the tactile action of puffing on a cigarette and the sensation of smoke in the mouth and throat [1]. Although not tested directly in the present study, the activity of other psychoactive substances in tobacco smoke that may strengthen nicotine dependence (such as acetaldehyde [2] or monoamine oxidase inhibitors [3]) may also play a role. There was no evidence of any excess adverse events in the intervention group.

One of the strengths of this study is that it was conducted in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines, was well-powered and outcome assessments were undertaken by researchers blind to treatment allocation. The study population was similar to Quitline callers and NZ smokers as a whole [24,25]. The trial had broad entry criteria, helping to ensure the generalizability of the findings. This generalizability is supported by the fact that the primary outcome was consistent, irrespective of the subgroups investigated. A number of limitations should be acknowledged. First, we did not verify self-reported abstinence biochemically, due to limited success with our previous cessation trials [17,26], and that attempts to validate quit status in population studies may introduce a selection bias unrelated to participants' smoking status [27]. Secondly, the study population drew upon a population that underrepresents Asian, Pacific Island, male, older and more dependent smokers [28], and Quitline callers may be more ready to quit than smokers identified from other sources [29]. Thirdly, the results of the *post-hoc* analyses should be interpreted with caution due to the potential for bias [30,31]. Fourthly, no definition of having 'smoked VLNC cigarettes' was provided to participants, thus we were unable to differentiate between participants who had had a few puffs, smoked only one to two cigarettes or smoked a larger number of the study cigarettes. Finally, some may question whether people increased puff frequency and intensity when smoking the VLNC cigarettes in an effort to maintain the desired level of nicotine [32]. Although compensatory smoking was not measured we feel it was unlikely, given the extremely low level of nicotine present in the study cigarettes and the concomitant provision of NRT. Becker *et al*. reported no compensatory smoking in the treatment group in their trial who received combination Quest 3 and NRT [4].

This trial provides strong evidence for the combined use of VLNC cigarettes, NRT and behavioural support as an effective smoking cessation strategy, and supports previous findings from the three smaller trials that investigated the use of RNCs in combination with NRT [4–6]. We observed no difference in the effect of the intervention according to specific subgroups, despite Becker *et al*. reporting that tapered use of Quest cigarettes and NRT had a greater effect on continuous abstinence at 4 weeks for women than for men [4]. Previous research has also shown that RNCs can suppress the signs and symptoms of nicotine withdrawal [7,27,33–37] and craving [7,33–37], due possibly to the automatic and non-automatic processes of drug-seeking behaviour and the non-nicotine components of tobacco smoke. We found no such effect in this trial when withdrawal and craving were measured using the MPSS, possibly because the time-points at which we measured these symptoms may have been too far into the period of abstinence. However, the use of the VLNC cigarettes resulted in a moderate effect on calming people and reducing irritability and craving when measured using the mCEQ, due possibly to the behavioural components of smoking cigarettes or to nicotine effects. When smoking a VLNC cigarette there is still sufficient nicotine to occupy, on average, 26% of the main nicotine acetylcholine receptors in the brain 3.1 hours after smoking, with occupancy likely to be higher immediately after smoking [38]. However, the low level of nicotine is insufficient to release dopamine, and thus there is little effect on smoking satisfaction [39]. The mCEQ was not asked at baseline, and thus we are unable to say how participants in the intervention group rated their level of satisfaction and craving reduction with the VLNC cigarettes compared to their regular brand. The lack of any significant difference in adverse events between the two groups in this trial has also been noted in earlier trials of RNCs [9], and contrasts with *in-vivo* research which postulated that RNCs may increase the risk of harm as 'cigarette nicotine modulates platelet activation *in vivo* in smokers' and therefore may 'moderate the risk of cardiovascular disease caused by non-nicotine smoke components' [40].

Complete cessation of all tobacco products confers the greatest health benefit to the individual. However, among smokers for whom safer smoking cessation interventions are contraindicated or have been tried unsuccessfully, our findings indicate that the use of a short course of VLNC cigarettes combined with NRT and behavioural support may be an option worth pursuing. Furthermore, the trial findings add weight to the idea of a stepped reduction in the nicotine content of cigarettes [41,42], or to an

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immediate and significant reduction of nicotine to a level where no compensation occurs [42], as a means to end smoking at a population level.

Clinical trial registration

This trial is registered with the Australasian Clinical Trials Network: number ACTRN12608000410358.

Declarations of interest

All authors declare that: (i) no authors have received support from any companies for the submitted work; (ii) C.B. and H.M. have previously undertaken research on behalf of NicoNovum, but prior to the purchase of the company by R. J. Reynolds. H.M. has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the manufacturers of smoking cessation medications. N.W. has provided consultancy to the manufacturers of smoking cessation medications, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation medications. M.G. has provided consultancy to the manufacturers of smoking cessation medications; (iii) their spouses, partners or children have no financial relationships that may be relevant to the submitted work; and (iv) all authors have no non-financial interests that may be relevant to the submitted work. The VLNC cigarettes used in the trial were purchased from Vector Group Ltd, Miami, FL, USA. The tobacco company had no role in development of the study design, data collection, data analysis, data interpretation or writing of the publication.

Acknowledgements

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Mainstream TNC Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11131R1

Project Code: **11131**
Project Start Date: **3-Aug-11**
Arista SOP #: **AM-001**
Smoking Protocol: **ISO**
Authorized By: **S. Simmons**
Title: **QA**

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run #	Port	Puffs (/cigt)	MS TPM (mg/cigt)	CO (mg/cigt)	Water (mg/cigt)	Nicotine (mg/cigt)	Tar (mg/cigt)
X22-B	16521	F00029	1	7.00	7.24	13.0	0.434	0.027	6.78
X22-B	16521	F00029	2	6.96	7.66	13.2	0.567	0.026	7.07
X22-B	16521	F00029	3	6.80	6.56	10.3	0.329	0.024	6.21
X22-B	16521	F00029	4	6.92	7.18	12.6	0.545	0.026	6.61
X22-B	16521	F00029	5	6.88	6.66	10.9	0.325	0.025	6.31
			Average	**6.91**	**7.06**	**12.0**	**0.440**	**0.026**	**6.59**
			SD	**0.077**	**0.452**	**1.29**	**0.115**	**0.001**	**0.350**
			%RSD	**1.11**	**6.40**	**10.8**	**26.2**	**3.71**	**5.30**
ACT-B	16522	F00029	7	8.38	8.80	11.2	0.418	0.671	7.71
ACT-B	16522	F00029	8	8.06	9.02	11.0	0.460	0.715	7.84
ACT-B	16522	F00029	9	9.02	9.92	11.9	0.574	0.776	8.57
ACT-B	16522	F00029	10	8.46	9.48	12.0	0.499	0.747	8.23
ACT-B	16522	F00029	11	8.40	9.42	11.6	0.684	0.716	8.02
			Average	**8.46**	**9.33**	**11.6**	**0.527**	**0.725**	**8.08**
			SD	**0.348**	**0.435**	**0.421**	**0.105**	**0.039**	**0.339**
			%RSD	**4.11**	**4.66**	**3.64**	**19.9**	**5.40**	**4.19**
Lab Control	3R4F	F00029	6	8.30	10.6	11.8	0.897	0.781	8.94
Lab Control	3R4F	F00029	12	8.14	10.0	11.3	0.750	0.740	8.47
			Average	**8.22**	**10.3**	**11.6**	**0.824**	**0.760**	**8.71**
			SD	**0.113**	**0.467**	**0.382**	**0.104**	**0.029**	**0.333**
			%RSD	**1.38**	**4.54**	**3.30**	**12.7**	**3.84**	**3.83**

Mainstream B[a]P Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11131R1

Project Code:	**11131**
Project Start Date:	**3-Aug-11**
Arista SOP #:	**AM-044**
Smoking Protocol:	**ISO**
Authorized By:	**A.Merson**
Title:	**QA**

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run #	Port	Arista Code	Puffs (/cigt)	MS TPM (mg/cigt)	B[a]P (ng/cigt)
X22-B	F00028	1	16521	7.10	7.02	3.29
X22-B	F00028	2	16521	7.00	7.10	3.33
X22-B	F00028	3	16521	6.90	6.90	3.06
X22-B	F00028	4	16521	6.88	6.98	2.96
X22-B	F00028	5	16521	6.80	6.38	3.12
			Average	**6.94**	**6.88**	**3.15**
			SD	**0.12**	**0.29**	**0.16**
			%RSD	**1.7**	**4.2**	**4.9**
ACT-B	F00028	7	16522	8.66	9.58	6.53
ACT-B	F00028	8	16522	8.48	9.74	6.61
ACT-B	F00028	9	16522	7.62	9.62	6.36
ACT-B	F00028	10	16522	8.48	9.92	6.75
ACT-B	F00028	11	16522	8.76	10.3	7.86
			Average	**8.40**	**9.8**	**6.82**
			SD	**0.45**	**0.3**	**0.60**
			%RSD	**5.4**	**3.1**	**8.7**
Lab Control	F00028	6	3R4F	8.30	11.1	6.78
Lab Control	F00028	12	3R4F	8.30	11.3	6.54
			Average	**8.30**	**11.2**	**6.66**
			SD	**0.00**	**0.1**	**0.17**
			%RSD	**0.0**	**1.3**	**2.5**

MS Smoke TSNAs Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11131R1

Project Code: 11131
Project Start Date: 3-Aug-11
Arista Method: AM-020
Smoking Regime: ISO
Authorized By: S. Simmons
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run #	Port	Puffs (/cig.)	MS TPM (mg/cig.)	NAB (ng/cig.)	NAT (ng/cig.)	NNK (ng/cig.)	NNN (ng/cig.)
X22-B	16521	F00030	1	7.00	6.46	1.23	6.40	12.2	55.4
X22-B	16521	F00030	2	7.32	7.88	1.38	6.53	13.9	59.0
X22-B	16521	F00030	3	6.72	6.64	1.56	5.96	12.3	54.8
X22-B	16521	F00030	4	6.86	6.80	1.34	6.69	16.1	57.9
X22-B	16521	F00030	5	7.00	6.30	1.38	6.45	14.1	57.3
			Average	**6.98**	**6.82**	**1.38**	**6.40**	**13.7**	**56.9**
			SD	**0.22**	**0.62**	**0.12**	**0.27**	**1.61**	**1.75**
			%RSD	**3.19**	**9.15**	**8.59**	**4.27**	**11.7**	**3.07**
ACT-B	16522	F00030	7	8.20	8.94	8.87	63.1	45.8	43.7
ACT-B	16522	F00030	8	8.30	9.22	8.62	66.8	45.3	50.0
ACT-B	16522	F00030	9	7.38	9.20	9.43	61.7	42.6	44.8
ACT-B	16522	F00030	10	8.08	8.78	6.05	43.8	40.1	36.2
ACT-B	16522	F00030	11	8.54	9.36	9.13	52.2	37.8	52.9
			Average	**8.10**	**9.10**	**8.42**	**57.5**	**42.3**	**45.5**
			SD	**0.44**	**0.23**	**1.36**	**9.34**	**3.41**	**6.44**
			%RSD	**5.39**	**2.58**	**16.1**	**16.2**	**8.05**	**14.1**
Lab Control	3R4F	F00030	6	8.28	9.98	15.5	119	107	123
Lab Control	3R4F	F00030	12	8.24	10.5	14.9	117	99.4	115
			Average	**8.26**	**10.2**	**15.2**	**118**	**103**	**119**
			SD	**0.03**	**0.37**	**0.41**	**1.37**	**5.05**	**5.31**
			%RSD	**0.34**	**3.59**	**2.69**	**1.16**	**4.90**	**4.46**

Mainstream B[a]P Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11137R1

Project Code: **11137**
Project Start Date: **24-Jun-11**
Arista SOP #: **AM-044**
Smoking Protocol: **ISO**
Authorized By: **S. Simmons**
Title: **QA**

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run #	Port	Puffs (/cigt)	MS TPM (mg/cigt)	B[a]P (ng/cigt)
X22 - A	16048	600626	2	6.90	7.32	3.46
X22 - A	16048	600626	3	6.76	7.20	3.40
X22 - A	16048	600626	4	6.80	6.84	3.26
X22 - A	16048	600626	5	6.66	7.16	3.36
X22 - A	16048	600626	6	6.96	7.22	3.43
			Average	**6.82**	**7.15**	**3.38**
			SD	**0.12**	**0.18**	**0.08**
			%RSD	**1.73**	**2.55**	**2.35**
ACT - A	16049	600626	8	8.26	9.56	6.81
ACT - A	16049	600626	9	8.40	10.1	6.86
ACT - A	16049	600626	10	8.40	10.3	6.98
ACT - A	16049	600626	12	8.54	9.94	6.76
ACT - A	16049	600626	13	8.74	9.96	7.46
			Average	**8.47**	**9.98**	**6.97**
			SD	**0.18**	**0.28**	**0.28**
			%RSD	**2.14**	**2.83**	**4.07**
Lab Control	3R4F	600626	7	8.26	9.68	6.29
Lab Control	3R4F	600626	11	8.34	10.0	6.36
			Average	**8.30**	**9.84**	**6.32**
			SD	**0.06**	**0.23**	**0.05**
			%RSD	**0.68**	**2.30**	**0.72**

MS Smoke TSNAs Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11137R1

Project Code: 11137
Project Start Date: 24-Jun-11
Arista Method: AM-020
Smoking Regime: ISO
Authorized By: S. Simmons
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run No.	Port	Puffs (/cig.)	MS TPM (mg/cig.)	NAB (ng/cig.)	NAT (ng/cig.)	NNK (ng/cig.)	NNN (ng/cig.)
X22 - A	16048	302022	2	7.18	7.64	1.92	7.48	15.7	62.4
X22 - A	16048	302022	3	7.16	7.38	1.20	6.08	14.0	62.4
X22 - A	16048	302022	4	7.20	7.30	1.52	8.52	16.0	67.2
X22 - A	16048	302022	5	7.14	7.08	1.52	6.20	16.8	64.9
X22 - A	16048	302022	7	7.14	7.16	1.16	6.60	14.5	63.9
			Average	**7.16**	**7.31**	**1.46**	**6.98**	**15.4**	**64.2**
			SD	**0.03**	**0.22**	**0.31**	**1.02**	**1.13**	**2.00**
			%RSD	**0.36**	**2.97**	**21.0**	**14.7**	**7.32**	**3.12**
ACT - A	16049	302022	8	8.52	9.76	10.7	84.6	59.1	69.0
ACT - A	16049	302022	9	8.86	10.6	11.0	85.3	57.8	67.8
ACT - A	16049	302022	10	8.64	10.1	9.36	85.1	58.6	64.9
ACT - A	16049	302022	11	8.68	9.84	10.6	87.7	65.9	71.4
ACT - A	16049	302022	12	8.96	10.3	10.5	85.3	55.1	65.5
			Average	**8.73**	**10.1**	**10.4**	**85.6**	**59.3**	**67.7**
			SD	**0.18**	**0.35**	**0.61**	**1.19**	**4.01**	**2.66**
			%RSD	**2.02**	**3.41**	**5.90**	**1.39**	**6.77**	**3.93**
Lab Control	3R4F	302022	6	8.08	10.1	12.8	119	96.7	112
Lab Control	3R4F	302022	13	8.18	11.0	13.4	130	94.6	130
			Average	**8.13**	**10.5**	**13.1**	**125**	**95.7**	**121**
			SD	**0.07**	**0.59**	**0.40**	**7.55**	**1.50**	**12.4**
			%RSD	**0.87**	**5.64**	**3.02**	**6.05**	**1.57**	**10.3**

ɱ TNC Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11253R1

Project Code: **11253**
Project Start Date: **7-Oct-11**
Arista SOP #: **AM-001**
Smoking Protocol: **ISO**
Authorized By: **S Burton**
Title: **QA**

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run #	Port	Arista Code	Puffs (/cigt)	MS TPM (mg/cigt)	CO (mg/cigt)	Water (mg/cigt)	Nicotine (mg/cigt)	Tar (mg/cigt)
X22-C	F00091	1	16931	7.4	8.3	13.0	0.580	0.029	7.71
X22-C	F00091	2	16931	7.2	8.1	12.6	0.508	0.028	7.58
X22-C	F00091	3	16931	7.1	7.9	11.3	0.324	0.025	7.51
X22-C	F00091	4	16931	6.9	7.0	12.1	0.316	0.026	6.68
X22-C	F00091	5	16931	7.3	7.7	12.7	0.520	0.027	7.15
			Average	**7.2**	**7.8**	**12.3**	**0.449**	**0.027**	**7.33**
			sd	**0.2**	**0.5**	**0.7**	**0.121**	**0.002**	**0.42**
			%RSD	**2.5**	**6.4**	**5.5**	**27.0**	**6.3**	**5.7**
ACT-C	F00091	7	16932	8.4	8.8	9.7	0.382	0.647	7.79
ACT-C	F00091	8	16932	8.2	9.6	11.0	0.443	0.655	8.48
ACT-C	F00091	9	16932	8.4	9.6	11.2	0.415	0.692	8.47
ACT-C	F00091	10	16932	8.3	9.6	10.6	0.450	0.688	8.42
ACT-C	F00091	11	16932	8.6	9.5	10.9	0.418	0.708	8.41
			Average	**8.38**	**9.4**	**10.7**	**0.422**	**0.678**	**8.32**
			sd	**0.16**	**0.3**	**0.6**	**0.027**	**0.026**	**0.29**
			%RSD	**1.9**	**3.5**	**5.5**	**6.4**	**3.8**	**3.5**
Lab Control	F00091	6	3R4F	8.4	10.5	10.6	0.771	0.760	9.01
Lab Control	F00091	12	3R4F	8.4	10.4	10.7	0.688	0.751	9.00
			Average	**8.41**	**10.5**	**10.7**	**0.729**	**0.756**	**9.00**
			sd	**0.01**	**0.1**	**0.1**	**0.059**	**0.006**	**0.01**
			%RSD	**0.2**	**0.7**	**0.9**	**8.1**	**0.8**	**0.1**

Mainstream B[a]P Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11253R1

Project Code:	**11253**
Project Start Date:	**7-Oct-11**
Arista SOP #:	**AM-044**
Smoking Protocol:	**ISO**
Authorized By:	**A.Merson**
Title:	**QA**

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Run #	Port	Arista Code	Puffs (/cigt)	MS TPM (mg/cigt)	B[a]P (ng/cigt)
X22-C	500702	2	16931	6.80	7.44	2.78
X22-C	500702	3	16931	7.10	7.66	2.94
X22-C	500702	4	16931	6.86	7.20	2.98
X22-C	500702	5	16931	7.22	7.52	2.82
X22-C	500702	6	16931	7.08	7.32	3.04
			Average	**7.01**	**7.43**	**2.91**
			SD	**0.18**	**0.18**	**0.11**
			%RSD	**2.51**	**2.39**	**3.71**
ACT-C	500702	8	16932	8.28	9.12	5.77
ACT-C	500702	9	16932	8.48	9.86	5.94
ACT-C	500702	10	16932	8.32	9.78	6.36
ACT-C	500702	11	16932	8.50	10.4	6.37
ACT-C	500702	12	16932	8.58	9.70	5.77
			Average	**8.43**	**9.78**	**6.04**
			SD	**0.13**	**0.47**	**0.30**
			%RSD	**1.51**	**4.81**	**5.02**
Lab Control	500702	7	3R4F	8.00	9.68	5.26
Lab Control	500702	13	3R4F	8.32	9.30	5.39
			Average	**8.16**	**9.49**	**5.32**
			SD	**0.23**	**0.27**	**0.09**
			%RSD	**2.77**	**2.83**	**1.75**

MS Smoke TSNAs Test Report for:
22nd Century Limited, LLC
8201 Main Street
Suite 6
Williamsville, NY 14221
United States
Q11253R1

Project Code: 11253
Project Start Date: 7-Oct-11
Arista Method: AM-020
Smoking Regime: ISO
Authorized By: S Burton
Title: QA

For questions or concerns, please see the customer feedback form at http://www.aristalabs.com

Client Code	Arista Code	Run No.	Port	Puffs (/cig.)	MS TPM (mg/cig.)	NAB (ng/cig.)	NAT (ng/cig.)	NNK (ng/cig.)	NNN (ng/cig.)
X22-C	16931	500703	2	6.82	6.82	1.36	6.88	11.63	56.62
X22-C	16931	500703	3	6.80	6.70	1.50	6.12	11.32	53.48
X22-C	16931	500703	4	6.68	6.62	1.58	6.91	12.51	54.39
X22-C	16931	500703	5	6.88	6.86	1.98	6.14	14.65	61.81
X22-C	16931	500703	6	6.50	7.22	1.78	6.06	11.65	60.78
			Average	**6.74**	**6.84**	**1.64**	**6.42**	**12.35**	**57.41**
			SD	**0.15**	**0.23**	**0.24**	**0.43**	**1.36**	**3.74**
			%RSD	**2.24**	**3.37**	**14.74**	**6.72**	**11.00**	**6.51**
ACT-C	16932	500703	8	8.36	8.68	9.70	71.13	52.62	50.36
ACT-C	16932	500703	9	8.46	9.06	10.64	76.96	53.91	59.43
ACT-C	16932	500703	10	8.28	8.64	9.39	70.13	49.13	51.79
ACT-C	16932	500703	11	8.28	9.30	9.36	73.76	46.26	55.73
ACT-C	16932	500703	12	8.04	9.38	9.40	74.60	46.01	53.79
			Average	**8.28**	**9.01**	**9.70**	**73.32**	**49.59**	**54.22**
			SD	**0.16**	**0.34**	**0.54**	**2.74**	**3.60**	**3.55**
			%RSD	**1.87**	**3.80**	**5.62**	**3.74**	**7.27**	**6.54**
Lab Control	3R4F	500703	7	8.20	9.38	15.81	133.43	93.16	122.47
Lab Control	3R4F	500703	13	8.30	8.94	13.03	120.69	95.59	114.11
			Average	**8.25**	**9.16**	**14.42**	**127.06**	**94.37**	**118.29**
			SD	**0.07**	**0.31**	**1.97**	**9.01**	**1.72**	**5.91**
			%RSD	**0.86**	**3.40**	**13.67**	**7.09**	**1.82**	**5.00**