Qualitative Study to Develop PARE / VLN Hypothetical Claims Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Smokers

Protocol Number:	5180077-0078-VLN-A1
Principal Investigator:	Randall Wahl Chief Research Officer M/A/R/C® Research 7850 North Belt Line Rd Irving, TX 75063
Sponsor:	22nd Century Group, Inc. 8560 Main Street Williamsville, NY 14221
Regulatroy Review:	Kinetiq 1501 Fourth Avenue Suite 800 Seattle, WA 98101
Version Number:	1.0
Date:	11-Nov-2018

SIGNATURE PAGE

Principal Investigator: I have read the protocol entitled "*Qualitative Study to Develop VLN Hypothetical Claims Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Smokers*" and agree to conduct the study as outlined in this document. In addition, I agree to conduct the study in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied by the Sponsor.

(b) (6) December 27, 2018

Randall Wahl, Chief Research Officer
M/A/R/C® Research

Date

(b) (6) December 27, 2018

Brad Seipel, Vice President
M/A/R/C® Research

Date

(b) (6) December 27, 2018

Lynn Dagar, Vice President
M/A/R/C® Research

Date

(b) (6) December 27, 2018

(b) (6) Research Director
M/A/R/C® Research

Date

TABLE OF CONTENTS

TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AS	Adult Smokers
CCs	Conventional Cigarettes
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CSIQ	Current Smokers with Intent to Quit
CSNIQ	Current Smokers with No Intent to Quit
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FFC	Full-Flavor Tasting Cigarettes
FG	Focus Group
HINTS	Health Information National Trends Survey
IDIs	In-Depth Interviews
IRB	Institutional Review Board
LA	Legal-Age
LTC	Light-Tasting Cigarettes
MRTP	Modified Risk Tobacco Product
NHIS	National Health Interview Survey
NRT	Nicotine Replacement Therapy
NSGP	Never Smokers General Population
NSLA	Never Smokers Legal-Age to 25
PI	Principal Investigator
PII	Personally Identifiable Information
PATH	Population Assessment of Tobacco Use and Health
PRI-P	Perceived Risk Instrument – Personal
RE	Reduced Exposure
REALM	Rapid Estimate of Adult Literacy in Medicine
RR	Reduced Risk
ULTC	Ultra-Light Tasting Cigarettes
US	United States
WHO	World Health Organization

STATEMENT OF COMPLIANCE

This study will be conducted in accordance with the specifications noted in the study protocol (Protocol Number: 5180078-00790-PARE/VLN™-A1; "*Quantitative Study to Develop VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Smokers*" and in accordance with The Insights Association's Code of Standards and Ethics for Marketing Research and Data Analytics.

1 KEY ROLES

Sponsor:
22nd Century Group, Inc.
8560 Main Street
Williamsville, NY 14221

Principal Investigator:
Randall Wahl
Chief Research Officer
M/A/R/C® Research
7850 North Belt Line Rd
Irving, TX 75063

Contract Research Organization:
M/A/R/C® Research
7850 North Beltline Road
Irving, TX 75063

Regulatory Review:
Kinetiq
1501 Fourth Avenue
Suite 800
Seattle, WA 98101

Protocol Author:
(b) (6)
Research Director
M/A/R/C® Research
7850 North Belt Line Rd
Irving, TX 75063

Lead Statistician and Data Manager:
Randall Wahl
Chief Research Officer
M/A/R/C® Research
7850 N. Beltline Road
Irving, TX 75063

2 INTRODUCTION: BACKGROUND

2.1 CANDIDATE MODIFIED RISK TOBACCO PRODUCTS (MRTPs)

While cigarette smoking among US adults aged 18 and older has declined to 15.5 percent in 2016 from 20.9 percent in 2005, nearly 38 million American adults continue to smoke conventional cigarettes (CCs) most days or every day (Centers for Disease Control and Prevention, 2018). Cigarette smoking causes damage to almost every organ in the body and results in premature death (U.S. Department of Health and Human Services, 2014). 22nd Century Group, Inc. (XXII) is developing a candidate Modified Risk Tobacco Product (MRTP) designed to aid current smokers in reducing the exposure to nicotine.

The complexity in developing an MRTP is creating a product that maximizes interest in the product as a substitute for Conventional Cigarettes (CCs) among Adult Smokers (while not dissuading them from the idea that they would be better off quitting smoking entirely), yet minimizes interest among Adult Never Users and Former Smokers. Further, it is imperative that these products do not negatively impact the Intention to Quit among Adult Smokers who have the Intention to Quit CCs.

The Qualitative Study to Develop VLN™ Hypothetical Product Messages focuses on a candidate MRTP product, menthol and non-menthol cigarettes (Figures 1 and 2. Pack Example Images; images for all packs in Appendix), planned to be commercialized under the brand name of “VLN™” (to be tested as both PARE and VLN™).

PARE / VLN™ cigarettes differ from CCs in that they are made with tobacco which has been genetically modified to contain 95% less nicotine than CCs, thereby lowering nicotine consumption. PARE / VLN™ cigarettes offer the same ritual properties of smoking and, while PARE / VLN™ may still pose the same health risks as CCs, conversion from CCs to PARE / VLN™ cigarettes significantly reduces Adult Smoker’s exposure to nicotine.

2.2 PARE / VLN™ CONSUMER PERCEPTION RESEARCH

Based on requirements of Section 911 of the Family Smoking Prevention and Tobacco Control Act and the FDA's recommendations as outlined in the Draft Guidance on Modified Risk Tobacco Product Applications (the "MRTP Draft Guidance"), XXII is conducting a broad program to study consumer perceptions in relation to PARE / VLN™.

The MRTP Draft Guidance states that: "FDA must ensure, for a risk or exposure modification order, that the advertising and messaging of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions." The MRTP Draft Guidance further states that MRTP applications should address the effect of the product, label, messaging and marketing material on (1) "Tobacco use behavior among current tobacco users," (2) "Tobacco use initiation among non-users (both never users and Former users)," and (3) "Consumer understanding and perceptions."

This *Quantitative Study to Develop VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Smokers* research will include:

- Three major sample cohorts and five separate groups of US consumers based on self-stated qualification
    - Adult Current Smokers (with statistically valid representation of both menthol and non-menthol users) divided into two groups:
        - With Intention to Quit
        - Without Intention to Quit
    - Adult Former Smokers divided into two groups based on length of cessation
        - Recent Quitters (within the past year)
        - Longer-term Quitters (more than one year of cessation)
    - Adult Never Smokers

Drawing on FDA reviews of prior MRTP submissions, this study will also measure number of cigarettes smoked per day to ensure inclusion of both light smokers (less than 10 cigarettes per day) and heavy smokers (10+ cigarettes per day). This study will also include subjects of Legal-Age (LA) to 25 years of age who have never smoked (Never Smokers) as a proxy for youth smokers who are not part of the study because they may not be interviewed without parental consent by law. For the purposes of this study, Legal-Age will be defined as the minimum age for tobacco purchase as determined by each participant's US state of residence.

The study will gather qualitative data addressing each of these areas of investigation with respect to PARE / VLN™ label and messaging involving modified risk and modified exposure claims.

The comprehensive research program has the following overall structure:

- Successive Four-Phase Qualitative Investigation to Develop and Refine VLN™ Label and Messaging
    - Development of the VLN™ label and messaging.
    - Qualitative Assessment of Comprehension of the VLN™ label and messaging.
    - Qualitative Assessment of Risk Perception of VLN™ based on the VLN™ label and messaging.
    - Evaluation of Future Intention to Use VLN™ based on the VLN™ label and messaging.
- Quantitative Study to Test VLN™ Label and Messaging for Comprehension, Risk Perception and Intention to Use Among Adult Smokers, Adult Former Smokers and Adult Never Users

2.3 DEFINITIONS OF LABEL AND MESSAGING

XXII has defined “label" and "messaging" for the program as a whole, as:

PARE / VLN "label"refers to the display of brand name text or graphical material, including branding on the pack containing VLN™ cigarettes, or the packaging box of VLN™ cigarettes.

PARE / VLN "messaging" refers to printed statements which accompany VLN™. For example, messaging could refer to text statements printed on the front, side or back of packaging containing VLN™ cigarettes.

2.4 VLN™ PRODUCT DESCRIPTION

PARE / VLN™ and PARE / VLN™ menthol are 84-millimeter cigarettes (sometimes called “shorts,” “regulars” or “kings”) and are made with the same components found in commercial brands of cigarettes such as a filter, cigarette paper and tobacco. PARE / VLN™ and PARE / VLN™ menthol are manufactured in a manner similar to that of a typical cigarette.

The tobacco in PARE / VLN™ cigarettes is different than the tobacco used in most cigarette brands. PARE / VLN™ cigarettes are made from a tobacco plant that has been altered to contain much lower levels of nicotine than the tobacco used in traditional cigarettes.

FIGURE 1. PARE PACK EXAMPLE IMAGE – NON-MENTHOL.

FIGURE 2. PARE PACK EXAMPLE IMAGE – MENTHOL.

FIGURE 3. VLN PACK EXAMPLE IMAGE – NON-MENTHOL.

FIGURE 4. VLN PACK EXAMPLE IMAGE – MENTHOL.

3 OBJECTIVES AND PURPOSE

3.1 DESIGN OVERVIEW

In addition to requiring that a modified risk tobacco product will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, the TCA requires that a modified risk tobacco product will benefit the health of the population as a whole, taking into account both users and non-users of tobacco products (TCA Section 911(h)(1)). The *Qualitative Study to Develop PARE / VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Smokers* is planned as a four-phase exploratory research initiative to develop claims messaging that effectively communicates the purpose of PARE / VLN™ to Current Smokers as well as Former Smokers and Never Users

Subjects will be categorized into four primary subject groups, based on self-reported smoking behavior:

- Group 1 – Adult Smokers with no Intention to Quit CCs
- Group 2 – Adult Smokers with the Intention to Quit CCs
- Group 3 – Adult Former Smokers
- Group 4 – Adult Never Smokers

Former Smokers and Current Smokers will be further divided based on cessation recency and Intention to Quit within the next six months, respectively. Among Current Smokers, light / social smokers and heavier smokers will both be profiled to ensure inclusion. In addition, a group of young Adult Never Smokers (from the legal smoking age to 25 years; "LA-25 Never Smokers") will be used, to enable the collection of sufficient data to describe responses within this group. Legal-Age will be defined as the minimum age for tobacco purchase as determined by each participant's US state of residence.

A baseline assessment of Risk Perception and future Intention to Use will be conducted on PARE / VLN™ and comparator objects.

In this research, all Comparator Categories will be assessed on Perceived Risk and Intent to Use by each subject prior to exposure to the PARE / VLN™ concept and messaging followed by the same assessment of PARE / VLN™ after exposure to the concept. In addition to these measurements, all PARE / VLN™ claims will be evaluated in direct comparison to each other. All comparator categories and products to be evaluated include:

- Type 1: Full-Flavor Tasting Cigarettes
- Type 2: Light Tasting Cigarettes
- Type 3: Ultra-Light Tasting Cigarettes
- Type 4: E-cigarettes
- Type 5: Moist Snuff
- Type 6: SNUS
- Type 7: Nicotine Replacement Therapies (NRTs)
- Type 8: Cessation

The product messages to be tested will vary by phase as messaging will be developed, refined and retested in each successive phase. Multiple messages will be tested including messaging on three key areas of each product package:

- Primary Claim
  - Placement: Front – Top of Pack
- Secondary (Comparative) Claim
  - Placement: Front – Top of Pack
- Disclaimer
  - Placement: Front – Bottom of Pack
- Back of Pack Language
  - Placement: Back – Top of Pack

Each subject will view one of four a Surgeon General's warnings on each pack: 1) “Smoking Causes Lung Cancer, Heart Disease, Emphysema And May Complicate Pregnancy.” 2) “Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.” 3) “Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight." 4) "Cigarette Smoke Contains Carbon Monoxide."

All messaing will be presented in a rotated order for each participant to avoid order bias. Rotation spreadsheets may be found in the Protocol #5180077-0078-PARE/VLN™-A1 Appendix.

3.2 PRIMARY GOALS

The primary objectives of this research include:

- Establish comprehension of messaging across all population samples, including low-literacy participants
- Evaluating consumer perception of and understanding surrounding proposed ad and pack messaging for Brand A (PARE / VLN™)
- Understanding perceptions of risk and communication of that risk through the statements on the pack

The scope of ad/pack messaging that was evaluated included:

- Primary Claim
- Secondary (Comparative) Claim
- Disclaimer
- Back of Pack Language

All ad/pack messages will be evaluated assuming all standard Surgeon General warnings for cigarettes are in place. Further, the claims tested will include both reduced risk and reduced exposure iterations. The proposed messaging includes multiple claims per phase.

3.3 SECONDARY GOALS

The secondary objectives of the study include:

- Unerstand perceptions among relevance populations (Adult Never Smokers, Adult Former Smokers, Adult Smokers Motivated To Quit, Adult Never Smokers LA-25)
- Assess risk perception for PARE / VLN™ and comparator objects
- Assess intent to use for PARE / VLN™ and comparator objects

** Legal-Age will be defined as the minimum age for tobacco purchase as determined by each participant’s US state of residence.*

4 SUBJECTS

4.1 DEFINITIONS

- Never Users
  - Adults who have not smoked at least 100 cigarettes in their entire life and currently do not smoke at all – plus currently do not use other tobacco or nicotine products and have never done so "fairly regularly"
- Former Smokers
  - Recent Quitters: Adults who have smoked at least 100 cigarettes in their entire life and currently do not smoke at all who indicate they completely quit smoking cigarettes less than 1 year ago
  - Long-Term Quitters: Adults who have smoked at least 100 cigarettes in their entire life and currently do not smoke at all who indicate they completely quit smoking cigarettes 1 year ago or more
- Current Smokers
  - Adult Smokers will be classified by Intention to Quit CCs (i.e. smokers with and without Intention to Quit CCs), based on Prochaska and DiClemente's Stages of Change Model (Prochaska and DiClemente, 1982)
    - With Intention to Quit: Adults who have smoked at least 100 cigarettes in their entire life and currently smoke every day or some days – and who respond "Yes" to a question regarding whether they are seriously considering quitting smoking cigarettes in the next 6 months
    - With No Intention to Quit: Adults who have smoked at least 100 cigarettes in their entire life and currently smoke every day or some days – and who respond "No" to a question regarding whether they are seriously considering quitting smoking cigarettes in the next 6 month
- LA-25 (Legal-Age to 25) Never Smokers
  - LA-25 Never Smokers are defined as Never Smokers between the legal smoking age to 25 years (inclusive).
  - This is included as an oversample of young Adult Never Smokers (from the legal smoking age to 25 years) to enable the collection of sufficient data to describe responses within this group.
  - These participants are being oversampled to ensure a proxy for participants below the regulated minimum age of purchase (under 18 years of age by federal law).
  - Legal-Age will be defined as the minimum age for tobacco purchase as determined by each participant's US state of residence.
  - Ensures representation among a critical sample subgroup without the unnecessary burden and potential ethical conflict of sampling an audience under the leal purchase age.

4.2 SUBJECT GROUPS

Subjects will offer self-reported smoking status as is consistent with prior research including the World Health Organization (WHO, 1998) and the The National Cancer Institute's Health Information National Trends Survey (HINTS).

The four main subject groups are defined as;

1. **Adult Smokers with no Intention to Quit CC:** Adult Smokers with no intention to Quit CC, in the pre-contemplation stage of Prochaska and DiClemente's Stages of Change model. This will include Regular Smokers.
2. **Adult Smokers with the Intention to Quit CC:** Adult Smokers in the contemplation and/or preparation stages of Prochaska and DiClemente's Stages of Change model. This will include Regular Smokers.
3. **Adult Former Smokers:** Adults who were previously regular smokers and, at the time of their participation in the study, quit CC more than 30 days ago.
4. **Adult Never Smokers:** Adults who have never smoked at all, or adults who have never been regular smokers and have smoked less than 100 cigarettes in their lives.

The National Cancer Institute's Health Information National Trends Survey (HINTS) and the Population Assessment of Tobacco and Health (PATH) survey both use 100+ cigarettes in a lifetime plus a question about current smoking behavior to define smokers and non-smokers / never users. The threshold of 100 cigarettes was initially established in three 1954/1955 studies on Veteran's mortality as well as a US population smoking supplement in the US Census Bureau's Current Population Study. The 100-cigarette threshold became a staple in determining smoking status was later used in the 1964 Adult Use of Tobacco Survey and the first US National Health Interview Survey (NHIS, 1965) where it became the key criterion for smoking status definitions.

4.3 SAMPLING

At a broad level, the sampling frame is adults living in the US. Across the four phases of research, a total sample size of 356 participants is deemed sufficient to provide feedback as claims messaging is developed and will allow for reporting of results by diverse population segments, including special relevance populations.

4.4 MAIN STUDY SAMPLING

All Focus Groups (FGs) will be homogenous in representation by age, gender and cigarette use. Total number of completed interviews will vary by phase as follows. The main samples will be stratified by the following.

1. **Smoking status**
   Each of the four main subject groups will be represented:
   1. Adult Smokers with No Intention to Quit CC
   2. Adult Smokers with Intention to Quit CC
   3. Adult Former Smokers
   4. Adult Never Smokers
2. **Gender**
   There will be a representative number of male and female subjects.
3. **Age**
   Each of the following age categories will be represented in each phase of the research:
   - Legal Age to 34 years
   - 35 to 49 years
   - 50+ years

4.4.1 SAMPLING FOR PHASE 1 – FOCUS GROUPS

- Phase 1 will include 12 groups for a total of N=72 respondents.
- Current Smokers will include representation by two groups:
  - Adult Smokers with no Intention to Quit CCs within the next 6 months
  - Adult Smokers with the Intention to Quit CCs within the next 6 months
- This first phase of research will include the target group of current smokers of cigarettes, both those not intending and those intending to quit (the latter, according to the CDC, represent approximately two-thirds of adult cigarette smokers).
- Groups will be homogenous by gender, age and smoking status, with each group containing a mix of regular and menthol users as well as a mix of full-flavor tasting vs. light-tasting cigarette smokers. Groups will also be distributed across markets to represent the 4 census regions.

Table 1. Phase 1 Sampling Plan

	Current Smokers With No Intention to Quit	Current Smokers With Intention to Quit
	Mix of Regular & Menthol Users, Proportionate to the Population	Mix of Regular & Menthol Users, Proportionate to the Population
LA-34, Male	1 group, M1	1 group, M3
35-49, Male	1 group, M2	1 group, M4
50+, Male	1 group, M3	1 group, M1
LA-34, Female	1 group, M4	1 group, M2
35-49, Female	1 group, M1	1 group, M3
50+, Female	1 group, M2	1 group, M4
TOTAL	**6 Groups**	**6 Groups**

4.4.2 SAMPLING FOR PHASE 2 – FOCUS GROUPS

- Phase 2 will include 30 FGs for a total of N=180 respondents divided equally by cigarette use status of Current Smokers and Former Smokers (n=90 per group).
- Current Smokers will include representation by two groups:
  - Adult Smokers with no Intention to Quit CCs within the next 6 months
  - Adult Smokers with the Intention to Quit CCs within the next 6 months
- Former Smokers will be represented by two groups:
  - Recent Quitters (quit within the past 12 months), who are at a greater risk of recidivism
  - Long-Term Quitters (quit longer than 12 months ago), who are at a lower risk of recidivism
- Each FG will be homogenous by gender, age and smoking status, with each group containing a mix of regular and menthol users as well as a mix of full-flavor tasting vs. light-tasting cigarette smokers. Groups will also be distributed across markets to represent the 4 census regions.

Table 2. Phase 2 Sampling Plan

	Current Smokers With No Intention to Quit		Current Smokers With Intention to Quit	Former Smokers	
	Regular Users	Menthol Users	Mix of Regular and Menthol Users, Proportional to Population	Recent Quitters (≤12 months)	Long-Term Quitters (>12 months)
LA-34, Male	1	1	1	1	1
35-49, Male	1	1	1	1	1
50+, Male	1	1	1	1	1
LA-34, Female	1	1	1	1	1
35-49, Female	1	1	1	1	1
50+, Female	1	1	1	1	1
Total	**6 Groups**	**6 Groups**	**6 Groups**	**6 Groups**	**6 Groups**

4.4.3 SAMPLING FOR PHASE 3 – IN-DEPTH INTERVIEWS

- Phase 3 will include 52 In-Depth Interviews (IDIs) to include Current Smokers, Former Smokers and Never Smokers.
- Never Smokers LA-25 will be included as a proxy for youth smokers to understand how this messaging affects this special population and how their interpretations or perceptions might be unique relative to the rest of the population.
- Current Smokers will include representation by two groups:
  - Adult Smokers with no Intention to Quit CCs within the next 6 months
  - Adult Smokers with the Intention to Quit CCs within the next 6 months
- Former Smokers will be represented by two groups:
  - Recent Quitters (quit within the past 12 months), who are at a greater risk of recidivism
  - Long-Term Quitters (quit longer than 12 months ago), who are at a lower risk of recidivism
- Groups will also be distributed across markets to represent the 4 census regions.

Table 3. Phase 3 Sampling Plan

	Current Smokers With No Intention to Quit		Current Smokers With Intention to Quit	Former Smokers		Never Users
	Regular Users	Menthol Users	Mix of Regular and Menthol Users, Proportional to Population	Recent Quitters (≤12 months)	Long-Term Quitters (>12 months)	Never Used Any Tobacco Products
LA-25, Male	-	-	-	-	-	2
26-34, Male	2	2	2	2	2	2
35-49, Male	1	1	1	1	1	1
50+, Male	1	1	1	1	1	1
LA-25, Female	-	-	-	-	-	2
26-34, Female	2	2	2	2	2	2

35-49, Female	1	1	1	1	1	1
50+, Female	1	1	1	1	1	1
TOTAL IDIs	8	8	8	8	8	12

4.4.4 SAMPLING FOR PHASE 4 – IN-DEPTH INTERVIEWS

- Phase 4 will include 52 In-Depth Interviews (IDIs) to include Current Smokers, Former Smokers and Never Smokers.
- Never Smokers LA-25 will be included as a proxy for youth smokers to understand how this messaging affects this special population and how their interpretations or perceptions might be unique relative to the rest of the population.
- Current Smokers will include representation by two groups:
  - Adult Smokers with no Intention to Quit CCs within the next 6 months
  - Adult Smokers with the Intention to Quit CCs within the next 6 months
- Former Smokers will be represented by two groups:
  - Recent Quitters (quit within the past 12 months), who are at a greater risk of recidivism
  - Long-Term Quitters (quit longer than 12 months ago), who are at a lower risk of recidivism
- Phase 4 will occur in only one location.

Table 4. Phase 4 Sampling Plan

	Current Smokers With No Intention to Quit		**Current Smokers With Intention to Quit**	**Former Smokers**		**Never Users**
	Regular Users	Menthol Users	Mix of Regular and Menthol Users, Proportionte to Population	Recent Quitters (≤12 months)	Long-Term Quitters (>12 months)	Never Used Any Tobacco Products
LA-25, Male	-	-	-	-	-	2
26-34, Male	2	2	2	2	2	2
35-49, Male	1	1	1	1	1	1
50+, Male	1	1	1	1	1	1
LA-25, Female	-	-	-	-	-	2
26-34, Female	2	2	2	2	2	2
35-49, Female	1	1	1	1	1	1
50+, Female	1	1	1	1	1	1
TOTAL IDIs	8	8	8	8	8	12

4.5 INCLUSION CRITERIA & STRATIFICATION

The study will be as inclusive as possible to be representative of the US population. However, certain groups, such as those who do not speak English with some level of proficiency or those under the age of 18, will be excluded. The sample will be stratified by smoking status and demographic criteria.

Quota sampling for FGs and IDIs by cigarette usage group and demographic variables will be utilized.

For example, participants will be screened for:

1. Ability to read and understand English*.
2. Currently residing in the US.
3. Legal age of purchase (defined as the minimum age for tobacco purchase as determined by each participant's US state of residence) or older.
4. Able and willing to comply with all study requirements.
5. Provides informed consent.

Sample will be further stratified into population subgroups based on a variety of characteristics including demographic criteria as well as current smoking status:

1. Number of cigarettes ever smoked.
2. Type of cigarette smoked (menthol/non-menthol)
3. Gender, ethnicity and annual household income to ensure representation consistent with the market.
4. Number of cigarettes smoked per day to ensure a mix of participants who are light / social smokers versus those who are heavier smokers.
5. Intent to quit smoking within the next year.
6. Cessation status - former smokers will be classified into recent versus long-term cessation.

4.6 EXCLUSION CRITERIA

Participants will be excluded from the research based on:

1. Past 3-month participation in any tobacco-related research.
2. Currently pregnant or breastfeeding or planning to become pregnant within the next 6 months.
3. Employees of tobacco or vapor companies, news or media, advertising / marketing, marketing research, healthcare, or attorney or paralegal, or having a first degree relative that is employed by these types of companies**.

**Only English-speaking participants will be recruited to participate as the product communication is only expected to be delivered in English at this time.*

***Employees, students and/or first-degree relatives of those who are employed by or pursuing education in sensitive industries will be excluded from the research to minimize bias and also to protect the proprietary product information that will be disclosed in the survey.*

5 PROCEDURES AND ASSESSMENTS

5.1 RECRUITMENT

Subjects will be recruited through proprietary databases aggregated by local recruitment facilities in the cities of interest for FGs / IDIs. Central testing facilities house proprietary databases and recruit participants who are profiled on basic demographic information which may be used in targeting potential subjects for inclusion into the study. Each participant will provide personally identifiable information (PII) to each facility but no PII for any participant will be released directly to the Contract Research Organization (CRO) or 22nd Century Group, Inc. All participants will be screened for demographic and cigarette use status.

5.2 SCREENING

Potential subjects will be called and asked to participate in a "Study About Products." Those who agree to participate will then be screened on the basis of the inclusion and exclusion criteria. The screening process will assess smoking status, age, gender, ethnicity and US Census Region. Eligible participants who fit the requirements of the sampling plan will pass the screener and be asked to participate in a focus group or in-depth interview at a central testing facility. Non-eligible participant's interviews will be immediately terminated and they will be thanked for their time. Potential subjects will be compensated an amount in line with the length of interview, US market research industry standards and region. Planned compensation by phase is:

Table 5. Participation Compensation by Research Phase

	Interview Legnth in Hours	Compensation Amount
Phase 1	2 hours 30 mins	$150
Phase 2	2 hours	$125
Phase 3	1 hour 15 mins	$100
Phase 4	1 hour 15 mins	$100

5.3 INFORMED CONSENT

Participants will be provided an informed consent form (ICF) to review and sign upon arrival and check-in at the central testing facility. Participants will be asked to review the informed consent information carefully and, at the conclusion of the form, will be asked if they agree to participate in the survey with an option to sign the form if they are in agreement or refuse signature and, thereby, participation. If they have signed the ICF, they will be allowed to participate in the interview; if not, they will be dismissed from participation.

Regardless of smoking status, all participants will view exactly the same ICF verbiage. This will prevent any bias or variance in responses based on the possibility that different messages were viewed. Subjects will be informed

that their participation is completely voluntary. Subjects will also be informed that they may voluntarily suspend or withdraw from participation at any time during the interview.

ICFs for each phase are available in Protocol #5180077-0078-PARE/VLN™-A1 Appendix.

5.4 SURVEY FLOW AND MEASUREMENTS

After passing all screening requirements and freely consenting to participation in the research, subjects be provided with a lobby survey to complete, a copy of each participant's photo identification and (if appropriate) cigarette pack.

All participants were screened to determine their literacy level using the Rapid Estimate of Adult Literacy in Medicine (REALM) screener. Efforts were made to include in the study those participants scoring less than 60 on the assessment, a score indicating a reading level at or below 8th grade.

Participants will then be escorted to a room to participate in FG or IDI and asked to give to the research staff their mobile phone, PDA, tablet, and any other electronic device that could be used to either record or photograph the research materials. These devices will be secured during the research and returned to the study participants as they are leaving the focus group room upon the completion of the research. All interviews will be audio recorded and transcribed for reference.

The following study materials will be prepared:

1. Product concept description, for each participant, of PARE / VLN™ product.
2. Print outs, for each participant, of the available product categories.
3. Print outs, for each participant, of the product claims.
4. Poster-sized (FGs) or 11 X 17 laminated printouts (IDIs) of scales to measure perceptions of:
    a. Risk of exposure to harmful compounds
    b. Risk of developing smoking-related diseases
    c. Intent to use

Phase 1 Discussion Guide Outline is noted below. Although this will be the basis for all qualitative interviews, the discussion guide is expected to evolve and be refined after each successive qualitative phase.

- Moderator Introduction
- Verbal Consent:
    - Verbal confirmation of receipt and signature of ICF from each participant
    - Verbal consent from each participant agreeing to participate in research and be recorded
- Confidentiality Explanation
- Research Introduction
    - Research Purpose
    - Identification of CRO and Sponsor
    - Why Participants Were Included
    - Ground Rules
- Group Introductions
- Detailed Review of Tobacco Products and Alternatives

  - Type 1: Full-Flavor Tasting Cigarettes
  - Type 2: Light Tasting Cigarettes
  - Type 3: Ultra-Light Tasting Cigarettes
  - Type 4: E-cigarettes
  - Type 5: Moist Snuff
  - Type 6: SNUS
  - Type 7: Nicotine Replacement Therapies (NRTs)
  - Type 8: Cessation
- Initial Evaluation of Tobacco Products and Alternatives
  - All comparator categories will be evaluated on:
  - Familiarity
  - Risk Perception
    - Likelihood of Exposure to Harmful and Potentially Harmful Compounds
    - Risk of developing smoking/tobacco related diseases
  - Intent to Use
- Presentation of Product Package with Messaging
  - Reduced Exposure (RE) Messaging*
    - Review each pack and all statements on each pack one at a time
  - Reduced Risk (RR) Messaging*
    - Review each pack and all statements on each pack one at a time

**Reduced Exposure and Reduced Risk message groups will be rotated to avoid order bias. All messaging will also be rotated to avoid order bias.*

    - Initial Reactions
    - Comprehension and Clarity of Messaging
    - Describe the benefits of the concept
    - Probing and discussion as is appropriate for the group
- Best of Claims Sets (Between and among RR / RE)
  - Select set of claims that most clearly or effectively describes the product benefits and associated risks
  - Risk Perception
    - Risk of Exposure to Harmful and Potentially Harmful Compounds
    - Risk of developing smoking/tobacco related diseases
  - Intent to Use
- Build Your Own Claims Set (Between and among RR / RE)
  - Create a set of claims from all presented (Primary, Secondary, that most clearly or effectively describes the product benefits and associated risks
  - Assess:
    - Clarity (specific words / phrases) & recommend changes
    - Product opinions based on “ideal set”
    - Actions participants would take upon exposure to product
    - Who is PARE / VLN™ intended for
    - Change in placement on Risk scales

    - Change in Intent to Use
- Wrap-Up
    - Review of disclaimers
    - Questions for moderator

5.5 INTERVIEW LENGTH

The study duration is expected to be approximately 1 hour and 15 minutes to 2 and a half hours for each subject dependent upon phase. This will be specified in the ICF.

5.6 WITHDRAWL FROM RESEARCH

As will be noted in the ICF, subjects may cease and withdraw from the research at any time of their choosing without penalty or loss of benefits. Subjects may do so by stating that they wish to withdraw or by leaving the room.

6 ANALYSIS CONSIDERATIONS

6.1 HYPOTHESES

The purpose of this study is to measure responses to versions of PARE / VLN™, a "Modified Risk Tobacco Product" (MRTP), and Control Products on label and messaging within populations of (1) Adult Smokers with an intention to quit, (2) Adult Smokers without any intention to quit, (3) Adult Former Smokers and (4) Adult Never Smokers.

The primary objectives of this research include:

- Establish comprehension of messaging across all population samples, including low-literacy participants
- Evaluating consumer perception of and understanding surrounding proposed ad and pack messaging for PARE / VLN™
- Understanding perceptions of risk and communication of that risk through the statements on the pack

6.2 ANALYSIS SAMPLES

Full Sample

All subjects invited to participate in the study who satisfy the inclusion and exclusion criteria, fully complete the survey and meet all data quality requirements will be included in the final sample.

Main Study Sample

The main study sample will include the four primary subject groups (Adult Never Smokers, Adult Former Smokers, Adult Current Smokers With Intent to Quit CCs, Adult Current Smokers With No Intent to Quit CCs) and a representative percentage of LA-25 Never Smokers. These participants must satisfy all inclusion and exclusion criteria to fully complete the survey and meet all data quality requirements.

LA-25 Never Smokers

The LA-25 Never Smokers sample will include those subjects in the main sample who are LA-25 Never Smokers as well as those who fulfill in the LA-25 "oversample." This group may be considered a fifth subject group.

6.3 ANALYSIS OF OBJECTIVES

Comprehension

No clear measurement precedent has been established for testing comprehension to market a tobacco product. Comprehension will be assessed using moderator discretion, in particular, based on perceptions among low-literacy participants to ensure recall and basic comprehension. Responses that target specific words or phrases cited by participants as being problematic will be presented in the final report.

Intent to Use Coparator Categories and PARE / VLN™

Qualitative assessments of each Comparator Category and PARE / VLN™ will be presented by subject group for each item related to Intent to Use. Intent to Use each comparator category will be assessed pre-exposure to PARE / VLN™ and post-exposure Intent to Use PARE / VLN™ will be reported.

Risk Perception

Perceived risk will be assessed by participants in two groups of attributes including (1) Risk of Exposure to Harmful Chemicals and (2) Risk of Developing Tobacco-Related Diseases. Responses will be presented by subject group for all Comparator Categories and PARE / VLN™.

7 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA / DOCUMENTS

The contract research organization (CRO) and PI will maintain documentation to permit evaluation of the conduct of the study, including assessing the quality and integrity of the study data and protection of human subjects. The PI will have access to all data from participants and will make these data available for inspection at the request of the Sponsor or regulatory agencies.

8 ETHICS / PROTECTION OF HUMAN SUBJECTS

8.1 ETHICAL STANDARDS

The PI has worked to ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46 and any additional human subjects protections as determined necessary.

8.2 INSTITUTIONAL REVIEW BOARD

Given the nature of this qualitative perception study and the limited opportunity for subject exposure to harm or risk, XXII Century Group, Inc. has declined IRB review and approval.

8.3 INFORMED CONSENT PROCESS

8.3.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent language describing in detail the study product(s), study procedures, and risks are given to the participant and documentation of informed consent is required prior to participant inclusion in the FG / IDI. The following consent materials are submitted with this protocol:

- Overview of the study and its purpose
- Informed consent language (Protocol #5180077-0078-PARE/VLN™-A1 Appendix)
- Participant Research Responsibilities & Risks of Cigarette Smoking/MRTPs

8.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Description of risks and possible benefits of participation will be provided to the participants in the ICF. Participants will be provided an informed consent form (ICF) to review and sign upon arrival and check-in at the central testing facility. Participants will be asked to review the informed consent information carefully and, at the conclusion of the form, will be asked if they agree to participate in the survey with an option to sign the form if they are in agreement or refuse signature and, thereby, participation. If they have signed the ICF, they will be allowed to participate in the interview; if not, they will be dismissed from participation.

Regardless of smoking status, all participants will view exactly the same ICF verbiage. This will prevent any bias or variance in responses based on the possibility that different messages were viewed. Subjects will be informed that their participation is completely voluntary. Subjects will also be informed that they may voluntarily suspend or withdraw from participation at any time during the interview without penalty or loss of benefits.

ICFs for each phase are available in Protocol #5180077-0078-PARE/VLN™-A1 Appendix.

8.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, the Sponsor and its agents. Therefore, the data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

Authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the PI, including the any data collected from participants in this study. The CRO will permit access to such records. At the end of the study, source documents / primary data will be securely maintained by the CRO for a minimum of five years after market authorization of a MRTP (or two years after formal discontinuation of development of the MRTP). Study participant data, which is for purposes of analysis and reporting, will be transmitted to and stored at 22nd Century Group, Inc. This will not include the participant's contact or other PII. Rather, individual participants and their research data will be identified by a unique study identification number. The study management systems used will be secured and password protected. At the end of the study, all study databases will be archived at 22nd Century Group, Inc.

9 DATA HANDLING AND RECORD KEEPING

9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All data captured from participants using manual or electronic systems will be stored in an electronic data capture (EDC) system. Data management will be responsible for reviewing these data as defined in the study protocol. The CRO is HIPAA compliant.

System access privileges will be strictly controlled and documented. Whenever any data are modified, a computer-generated audit trail will be generated.

9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 5 years after the authorization of a MRTP application or until at least 2 years have elapsed since the formal discontinuation of development of the MRTP. These documents should be retained for a longer period, however, if required by regulations. No records will be destroyed without the written consent of the Sponsor, if applicable.

9.3 PROTOCOL DEVIATIONS

A protocol deviation is any nonadherence with the study protocol. The nonadherence may be either on the part of the participant, the PI, or the other study staff. As a result of deviations, corrective actions are to be developed by the PI in consultation with the Sponsor and implemented promptly.

9.4 PUBLICATION AND DATA SHARING POLICY

Participant responses will be kept confidential. Data could be shared with other entities only when: 1) the participant gives explicit permission to release this data, or 2) data are shared with an entity who agrees in writing that the data will be held strictly confidential and that the data will be used for research purposes only, or 3) the release of this data is required by a regulatory agency.

These data are being collected to support an MRTP application for VLN™. Any publications arising from this work will report data in aggregate form and will not include any PII.

10 CONFLICT OF INTEREST POLICY

None.

11 PROTOCOL REVISIONS

Version	Date	Significant Revisions

APPENDIX

Study Name:	Qualitative Study to Develop PARE / VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Smokers
Protocol Number:	5180077-0078-VLN-A1
Sponsor:	22nd Century Group, Inc. 8560 Main Street Williamsville, NY 14221
Version Number:	1.0
Date:	11-Nov-2018

For all appendices, please refer to Appendices: 5180077-0078-VLN-A1 – Qualitative Study to Develop PARE / VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Smokers