PROTOCOL

Title of Study: Randomized, Parallel Group, Assessor-Blind Study to Evaluate the Oral Mucosal Effects in Healthy Adult Smokers Associated with 3 Weeks of Use of Niconovum Nicotine Bitartrate 4 mg Mint Lozenge Relative to the GSK Nicorette® Nicotine Polacrilex 4 mg Mint Lozenge.

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Study Objectives:	Primary • To assess the oral mucosal health associated with 3 weeks of use of test product, Nicotine Bitartrate 4 mg mint lozenge (Niconovum), relative to a reference product, Nicorette® [Nicotine Polacrilex] 4 mg mint lozenge GlaxoSmithKline (GSK), in healthy adult smokers motivated to quit smoking. Secondary • To evaluate the safety and tolerability of Nicotine Bitartrate 4 mg mint lozenge and Nicorette® [Nicotine Polacrilex] 4 mg mint lozenge in this subject population.
Design of Study:	This will be a randomized, parallel group, assessor-blind, 3-week, safety study in which 100 healthy adult smokers motivated to quit smoking will be instructed to use 9 - 20 lozenges per day over the course of the study. Subjects will be randomized on a 1:1 treatment with Nicotine Bitartrate 4 mg mint lozenge (test) or Nicorette® Nicotine Polacrilex 4 mg mint lozenge (reference).
Randomization	Subjects will be randomized in a 1:1 ratio to receive either nicotine bitartrate 4 mg mint lozenge (Test Product) or Nicorette® 4 mg mint lozenge (Reference Product). It is expected that 100 subjects (50 in each group) will be randomized in the study at a single study site. Randomization will be stratified by smoking status so that in each treatment group a minimum of 10% of the subjects will be smokers of ≥ 30 cigarettes/day, and a minimum of 40% of the subjects will be smokers of 20 - 29 cigarettes/day.
Test product	Nicotine Bitartrate 4 mg mint lozenge
Reference product	GSK Nicorette® [Nicotine Polacrilex] 4 mg mint lozenge
Treatment groups	Eligible subjects meeting all study criteria will be randomized equally to receive one of the following treatments: • Niconovum Nicotine Bitartrate 4 mg mint lozenge

	• Nicorette® [Nicotine Polacrilex] 4 mg mint lozenge
Criteria for Inclusion:	Potential subjects who meet the following criteria at Screening may be included in the study. 1. Sex and Age: Males and females aged at least 18 years and older. 2. Informed of the nature of the study and have agreed to and are able to read, review, and sign the informed consent document prior to commencing any study specific procedures. The informed consent document will be written in English, therefore the volunteer must have the ability to read and communicate in English. 3. Must have smoked at least 10 cigarettes per day for the previous 12 months prior to screening. 4. Must smoke first cigarette within 30 minutes of waking up. 5. Must be motivated to quit smoking upon enrollment into the study. 6. Contraception: Females of childbearing potential who have been, in the opinion of the Investigator, practicing a reliable method of contraception for at least two months prior to study participation and must agree to remain on an acceptable method of contraception while participating in the study period using the study medication. Acceptable methods of contraception are hormonal birth control, intrauterine device, double barrier methods, vasectomized partner or abstinence. 7. Females of childbearing potential will be required to undergo a serum (Screening) and urine (Day 0) pregnancy test (must be negative). 8. Females of non-childbearing potential must be surgically sterile for at least three months prior to Screening or post-menopausal for at least two years. 9. General health: All study participants must have good general health and no impairment that would impede or affect ability to participate in the study as deemed acceptable by the Investigator.

	10. Compliance: All study participants must understand and be willing to comply with all study procedures and restrictions. 11. Consent: All study participants must demonstrate willingness to participate as evidenced by voluntary written informed consent and must have received a signed and dated copy of the informed consent form.
Criteria for Exclusion:	1. Females who have a positive pregnancy test, are pregnant, breastfeeding, or intend to become pregnant during the course of the study. 2. Nicotine use: a) Is unable/unwilling to stop using forms of tobacco (e.g., traditional cigarettes, chewing tobacco, nicotine gels, cigars, snuff tobacco, nicotine patch and electronic cigarettes) for the duration of the study. b) Is unable/unwilling to stop using other nicotine replacement therapy products throughout the duration of the study. 3. Disease: Has a medical history, which in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results, e.g., known history of heart disease, recent myocardial infarction or cerebrovascular accident (i.e., within 12 weeks prior to enrollment), unstable angina, severe cardiac arrhythmia, diabetes or peptic ulcer. 4. Demonstrates a reactive screen for Hepatitis B surface antigens, hepatitis C antibody, or HIV antibody. 5. Oral condition: a) Has history of oral surgery (including extractions) within four weeks of screening, operative dental work within seven days of screening, or a presence of any clinically significant oral pathology (as determined by an oral health professional – dentist or dental hygienist) including lesions, sores or inflammation of the mouth which would interfere with study assessments or confound the results.

	b) Has fixed retainers, orthodontic appliances, or either maxillary and/or mandibular dentures or other appliances which may interfere with the placement of the product. c) Has current or recurrent disease that could affect the site of application, the action, absorption of the study treatment, or clinical assessment. d) Has severe gingivitis, periodontitis or rampant caries (extensive dental decay, i.e., big/deep cavities, in many teeth), as diagnosed by an oral health professional- dentist or dental hygienist. e) Has the presence of oral or peri-oral ulceration including herpetic lesions at screening (subjects with these lesions may be re-examined at a subsequent appointment and may be able to be admitted at a later date if the ulceration or herpetic lesion heals) or Study Visit Day 0. f) Has elective dentistry scheduled during the study duration. 6. Allergy/Intolerance: a) Has a known or suspected intolerance or hypersensitivity to the study materials (or closely-related compounds) or any of their stated ingredients. b) Has a known genetic deficiency with an inability to metabolize aspartame or phenylalanine or has been diagnosed with phenylketonuria. 7. Clinical Study Participation: a) Participation in another clinical study or receipt of an investigational drug within 30 days of the screening visit at the start of the study. b) Previous participation in this study. 8. Substance abuse: a) Current or recent (within two years of screening) history of drug or alcohol abuse, misuse, physical or psychological dependence. b) Demonstrates a positive alcohol breath test.

	c) Demonstrates a positive urine drug screen without disclosure of corresponding prescribed concomitant medication(s) at Screening and Study Visit Day 0. 9. Urine glucose: a) Positive glucose urine screen. 10. Personnel: a) Is an employee of the Sponsor or the study site. b) Is a member of the same household as another subject in this trial. 11. Use of all over the counter (OTC) and prescription (Rx) lozenges after starting the study (Day 0 and onward).
Investigation Site	One study center within the United States. One screening center in the United States.
Study Duration:	Screening period up to 3 weeks; treatment period 3 weeks with follow-up visit 3 days after last dose.
Primary Endpoint	OMI-20 Total score change from baseline (Day 0) at each study visit (Days 3, 7, 14 and 21) in the Modified-Intent-to-Treat (mITT) population.
Secondary Endpoints	<u>In specified subpopulations:</u> • OMI-20 Total score change from baseline (Day 0) at each study visit (Days 3, 7, 14 and 21). <u>In all populations:</u> • OMI-20 Erythema subscore change from baseline at each study visit (Days 3, 7, 14 and 21) • OMI-20 Ulcer subscore change from baseline at each study visit (Days 3, 7, 14 and 21). <u>Safety Endpoints:</u> Other safety endpoints measured at study visits (Days 3, 7, 14 and 21 as applicable): • Clinical laboratory assessments (clinical chemistry; hematology; serology; urinalysis) • Vital signs • 12-lead Electrocardiogram (ECG) • Analysis of biopsied materials (if any) and adverse events (AE) assessment.

	Recovery Assessments: • OMI-20 Total score Day 24 versus Day 21 • OMI-20 Erythema score Day 24 versus Day 21 • OMI-20 Ulcer score Day 24 versus Day 21 • Safety endpoints Day 24 versus Day 21
Statistical Methods	Modified Intent-to-Treat (mITT) Population: The mITT population will include all subjects who were randomized and used at least 1 lozenge. This will be the main population for analysis. Per-Protocol (PP) Subpopulation: The per-protocol population will be a subset of the mITT population and will consist of subjects who complete the study without any major protocol deviations, as determined by clinical review. Examples of major protocol deviations: • CO levels exceeding 10 ppm at one or more study visits • Used < 9 or > 20 lozenges/day on more than 2 study days Heavy Lozenge Use Subpopulation: The heavy lozenge use population will be a subset of the mITT population and will consist of subjects who use an average of 15 or more lozenges per day (irrespective of completion of the study). Concomitant Smoker Subpopulation: The concomitant smoker population will be a subset of the mITT population and will consist of subjects who either admit smoking during the study or who have a CO > 10 ppm at any study day excluding Day 0 or Day 24 that cannot otherwise be explained. Oral Mucosal Safety Assessment: OMI-20 assessments are based on change from baseline values. At each time point, the OMI-20 will be evaluated for each group using group mean and SD of all test product subject scores. The assessments will be conducted by a dental hygienist. • OMI-20 Total (Range 0-60) • OMI-20 Erythema (Range 0-27)

	• OMI-20 Ulcer (Range 0-27) Statistics - This data will be presented for Days 0, 3, 7, 14, 21 and 24 by treatment group as continuous data (mean, median, standard deviation, minimum, maximum). A high score would indicate worse oral health. Data will be presented according to the number of subjects remaining in the study at each visit. Data will not be imputed. <u>Primary Endpoint Analyses:</u> The primary endpoint change from baseline (Day 0) compared to each study visit day (Days 3, 7, 14 and 21) in OMI-20 total score will be summarized using descriptive statistics (mean, standard deviation, minimum, maximum, median) and presented by treatment group using mITT populations. No formal comparisons between groups will be conducted. <u>Secondary Endpoint Analyses</u> The change from baseline in erythema and ulcer subscores will be summarized using descriptive statistics (mean, standard deviation, minimum, maximum, median) and presented by treatment group using the mITT population. The change from baseline (Day 0) compared to each study visit day (Days 3, 7, 14 and 21) in OMI-20 total score, erythema subscore, and ulcer subscore will be summarized using descriptive statistics (mean, standard deviation, minimum, maximum, median) and presented by treatment group for the following subpopulations: • Per protocol population • Heavy lozenge use subpopulation • Concomitant smoker subpopulation No formal statistical comparisons between treatment groups will be conducted. For other parameters, continuous data will be summarized using descriptive statistics (mean, standard deviation, minimum, maximum, median) to aid the data interpretation at each study visit:

	Adverse events and other categorical variables will be tabulated by the number and % of subjects experiencing the event by treatment group. Other indicators will include severity, seriousness and relationship to study drug by treatment group. No formal statistical comparisons between treatment groups will be conducted. Recovery will be assessed by comparing OMI-20 total score, erythema subscore, ulcer subscore and all safety endpoints on Day 24 versus Day 21. <u>Compliance</u> • Breath carbon monoxide levels will be presented by subject for each visit and will be used to identify concurrent smokers (CO > 10 ppm) and to stratify results of compliant and noncompliant subjects. • Average number of lozenges used per day will be tabulated. Reasons for lozenge use of < 9 or > 20 lozenges per day will be collected at each visit and presented by treatment group and by visit.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	Term or Definition
°C	Celsius
°F	Fahrenheit
ACTH	Adrenocorticotropic hormone
ADL	Activities of Daily Living
AE	Adverse Event
BP	Blood Pressure
CFB	Change from baseline
CFR	Code of Federal Regulations
cm	Centimeters
CO	Carbon Monoxide
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EOT	End of Treatment
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePDAT®	Electronic Patient Data Acquisition Tablet
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IRB	Institutional Review Board
kg	Kilograms
L	Liters
mg	Milligrams
mITT	Modified-intent-to-treat
NCI	National Cancer Institute
NRT	Nicotine Replacement Therapy
OMI	Oral Mucositis Index

OTC	Over the counter
pH	A measure of the acidity or alkalinity of a solution
PI	Principal Investigator
PP	Per protocol
ppm	Parts-per-million
RAISC	RAI Services Company
RAI	Reynolds American Inc.
RBC	Red blood cell count
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure