JOHNSON & JOHNSON CONSUMER INC.

SUMMARY CLINICAL STUDY REPORT

PROTOCOL TITLE:	Two-Week Clinical Safety and Saliva Flow Quantification
PROTOCOL NUMBER:	CCSORC005121 Amendment 1_02 Dec 2022
SPONSOR:	Johnson & Johnson Consumer Inc. [redacted]
STUDY SITE:	Salus Research, Inc. 1220 Medical Park Drive, Building 4 Fort Wayne, Indiana 46825 [redacted]
PRINCIPAL INVESTIGATOR:	Jeffery Milleman, DDS, MPA [redacted]
KEY SITE STAFF	Sub-Investigator: Kimberly Milleman, RDH, PhD [redacted] Study Director (SD) / Designated Physician Representative (DPR) (until 26 January 2023): Mary Lynn Bosma, RDH, DDS Director Oral Health, Medical Affairs and Clinical Research [redacted] SD/DPR (starting 26 January 2023): Patricia Gorecki, DMD, PhD, MOralSurg Clinical Strategy Director, Oral Healthcare [redacted] Statistician: Tony McGuire, Director Global Biostatistics [redacted] Study Manager: Alicia DelSasso, CCRP [redacted]
STUDY INITIATION DATE (First Subject First Visit):	28 Nov 2022
STUDY COMPLETION DATE (Last Subject Completed):	16 Dec 2022

SITE APPROVAL:	[redacted]
SPONSOR REVIEW AND APPROVAL:	[redacted]

The principles of the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP E6 (R2)) were applied to this study.

TABLE OF CONTENTS

1. STUDY SYNOPSIS

The principles of the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP E6 (R2)) were applied to this study.

INTRODUCTION	The irritation potential of new ingredients in mouth rinse formulations is assessed via oral soft and hard tissue tolerance trials. This clinical trial was designed to address two experimental oral care mouth rinse formulations and two marketed control formulations compared to brushing only (no mouth rinse) on oral tissue conditions in adults after using for two weeks. These experimental formulations were either alcohol-containing or alcohol-free and contained zinc, which is an inactive ingredient used in mouth rinses for tartar and malodor control. In addition, as a secondary endpoint this trial addressed short term salivary flow and pH after a single use of the assigned mouth rinse regimen.
OBJECTIVE	The purpose of this clinical trial was to evaluate the oral soft and hard tissue tolerance after 14 days of a twice-daily regimen of tooth brushing, then rinsing with an assigned essential oil-containing mouth rinse versus a control of brushing only. In addition, the trial assessed the volume and pH of saliva generated after a single use of the assigned regimen of brushing followed by rinsing with their assigned essential oil-containing mouth rinse compared to brushing followed by a water rinse. The primary endpoint was oral tolerance based on oral hard and soft tissue exams at three and 14 days of the trial and safety assessments through adverse event monitoring. The secondary endpoints were changes in the salivary flow rate and pH after a single use of the assigned regimen (brushing/rinsing with assigned mouth rinse) versus the control regimen (brushing/rinsing with water) at these timepoints: 0 minutes (for salivary flow only), then 2, 5, 10, 15 and 30 minutes.
STUDY DESIGN	This was a two-week, single center, examiner-blind, randomized, parallel-group controlled clinical trial. The trial protocol [redacted] provides the complete trial design.
SUBJECT INFORMATION	The complete eligibility criteria for this study were followed as defined in the study protocol [redacted].

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<td>INVESTIGATIONAL STUDY MATERIALS</td>
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<tr><th>Identification</th><th>UPC/Formula Number</th><th>Product Type</th></tr>
<tr><td>LISTERINE® Cool Mint® Antiseptic Mouthwash (abbreviated LCM)</td><td>UPC# 312547427357</td><td>Investigational Product (IP)</td></tr>
<tr><td>LISTERINE® ULTRACLEAN® Tartar Control Antiseptic Mouthwash Cool Mint® (abbreviated LUT)</td><td>UPC# 312547422673</td><td>IP</td></tr>
<tr><td>Listerine Advanced Gum Alcoho[redacted] (abbreviated LAG-Alcohol)</td><td>[redacted]</td><td>IP (Experimental)</td></tr>
<tr><td>Listerine Advanced Gum Zero (abbreviated LAG-Zero)</td><td>[redacted]</td><td>IP (Experimental)</td></tr>
<tr><td>Colgate® Cavity Protection Toothpaste</td><td>UPC# 035000510853</td><td>Auxiliary Product</td></tr>
<tr><td>Colgate® Full Head/Soft Bristles Toothbrush</td><td>UPC# 035000550101</td><td>Ancillary Product</td></tr>
<tr><td>Reach® Unflavored Waxed Dental Floss</td><td>UPC# 381370092131</td><td>Ancillary Product</td></tr>
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<td>DOSE AND MODE OF APPLICATION</td>
<td>There were five arms in this trial:
1. Brush / LCM mouth rinse
2. Brush / LAG-Alcohol mouth rinse
3. Brush / LAG-Zero mouth rinse
4. Brush / LUT mouth rinse
5. Brush Only (control group, abbreviated as BO)

All subjects were instructed to brush their teeth twice daily for one timed minute using the toothpaste and soft bristled toothbrush provided. They were instructed to place a full ribbon of toothpaste across the length of the provided toothbrush.

Subjects in the four groups that used mouth rinse were instructed to rinse with 20mL of their assigned mouth rinse for 30 timed seconds, following label instructions, after each brushing.

The first product use (brushing and rinsing) was conducted at the site under supervision of study personnel. All other brushing and rinsing was unsupervised. Subjects recorded each brushing and rinsing on their subject diary card.</td>
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<td>METHODOLOGY</td>
<td>For each study visit, subjects presented to the clinical site after refraining from using oral hygiene products for at least four hours, but no more than 12 hours, and refraining from eating, drinking (including water) and smoking for at least one hour prior to the visit.</td>
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	Visit 1: Day 0 – Screening/Baseline Subjects were consented, had their prior and concomitant medications/non-drug therapies, smoking, medical and dental histories and inclusion and exclusion criteria reviewed. Female subjects of childbearing potential were given a urine pregnancy test. Subjects were required to fill out the site's IRB approved Implementation of COVID-19 Prevention Procedures Consent Form. Subjects were asked to bring a list of their current medications and supplements and their current toothpaste and mouthwash (if applicable) with them. Site personnel recorded the brand/toothpaste name and how long they had been using that specific brand/toothpaste name. Site personnel also recorded the brand and name of mouthwash used (if applicable) and how long they had been using that specific brand/mouthwash. Resting unstimulated saliva samples were collected after subjects sat quietly for five minutes. During the timed five-minute collection period, subjects were instructed to allow their saliva to pool, emptying it into a collection vial whenever they feel the need to swallow. Subjects were not allowed to talk or read or use their cell phones to avoid distraction from providing the sample. Upon completion of the five minutes, the final amount of saliva was weighed, flow rate was determined and expressed as mL/min. Flow rate had to be 0.3 mL/min or greater. Salivary pH was measured. After the initial saliva collection, subjects had oral hard and soft tissue assessments and assessments of other inclusion/exclusion criteria to complete their study qualification. Qualifying subjects were randomly assigned to one of five study arms. Subjects were given their study toothbrush, toothpaste, mouth rinse (if applicable), floss (if flossing was part of their normal oral hygiene routine), and subject diary/instruction card. Subjects in the BO group brushed their teeth with the assigned toothpaste for one timed minute, expectorated into a collection tube for 10 seconds, rinsed with 20mL of tap water for 30 seconds and then expectorated into the same collection tube for 20 seconds. This was the immediate (0 minute) collection timepoint for the brush only group. Subjects in the brush/rinse groups brushed their teeth with the assigned toothpaste for one timed minute, expectorated into a collection tube for 10 seconds, rinsed with 20mL of their assigned mouthwash for 30 seconds and then expectorated into the same collection tube for 20 seconds. This was the immediate (0 minute) collection timepoint for the brush/rinse groups. Following the initiation of product use, timed two-minute saliva samples were collected from each subject into separate collection vials at the following time points: 2, 5, 10, 15 and 30 minutes. The salivary flow rate (expressed as

	mL/min) and weight (expressed as g) were determined and recorded at each collection timepoint. Salivary pH was measured at baseline (before product use) and then 2, 5, 10, 15 and 30 minutes after the initiation of product use. Adverse events (AEs) were assessed, and the next visit was scheduled. **Visit 2: Day 3 ± 1 day** Hard and soft tissue tolerance was evaluated. Compliance was evaluated by weighing residual volumes of returned mouth rinse (if applicable), visually inspecting toothpaste tubes to ensure proper use and reviewing the subject diary cards. AEs were assessed and the next visit was scheduled. **Visit 3: Day 14 ± 1 day** Hard and soft tissue tolerance was evaluated. Female subjects of childbearing age were given a urine pregnancy test. Compliance was evaluated by weighing residual volumes of returned mouth rinse (if applicable), visually inspecting toothpaste tubes to ensure proper use and reviewing the subject diary cards. AEs were assessed and subjects were dismissed. --- Subjects were instructed to use only the products given to them throughout the trial. No other oral hygiene procedures were permitted, including teeth cleaning, whitening or dental procedures except for an emergency treatment. The decision to withdraw a subject due to emergency dental treatment was at the discretion of the investigator. --- **Statistical methods:** Safety analysis including oral hard and soft tissue exams and AEs is based on the Safety Analysis Set. The number and percentage of subjects with treatment-emergent AEs and those experiencing investigational product-related AEs were tabulated. A summary tabulation of conditions and irritation scores by anatomical site based on the oral examinations was presented by visit and by investigational product. The analysis on saliva flow rate and pH measurement was based on the Full Analysis Set. Pairwise comparisons between investigational products are based on a mixed-effects model for repeated measures analysis (MMRM), including terms for investigational product and timepoint, and the baseline value as a covariate. Investigational product-by-timepoint and baseline-by-timepoint terms were included to compare investigational products at specific timepoints. The within-subject correlation structure was specified as unstructured. Comparisons were made for each mouth rinse group vs the BO group.

MEASUREMENT AND/OR EVALUATION SCHEDULE	Hard and soft oral tissue tolerance and AEs were assessed at all site visits. Saliva samples were collected at visit 1 only.
INSTITUTIONAL REVIEW BOARD (IRB)	This study was reviewed and approved by the following IRB: - Veritas IRB Inc. - (866) 384-4221 - info@veritasirb.com - Approval date: 14 Nov 2022 Applicable Amendments: Protocol Amendment 1 dated 02 Dec 2022 Approval date: 08 Dec 2022
SAFETY AND ADVERSE EVENTS	Oral tissue tolerance was monitored through oral exams and the collection of AEs. Safety was assessed through observation and query of each subject at each visit during the study for any new or continuing symptoms since the previous visit and through the tabulation of AEs. Details of AEs including resolution were captured. Any intra-oral AEs were photographed and sent to the Sponsor.
MONITORING, QUALITY CONTROL, AND QUALITY ASSURANCE	The study monitoring was conducted as per the Sponsor's requirements. The study site was subject to review by the IRB, quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities.
CONCLUSION	The results of this two-week clinical trial show that the irritation potential as measured by oral hard and soft tissue tolerance and AEs of the four mouth rinse formulations used in a twice-daily oral care regimen of brushing followed by rinsing with the assigned mouth rinse was similar to a twice-daily oral care regimen of brushing only. Additionally, the irritation profiles of the two experimental mouth rinses that contained zinc, with and without alcohol, were similar to the irritation profile seen with mouth rinses that are currently marketed for the control of plaque, gingivitis and calculus. All the mouth rinses in this trial significantly increased salivary flow rate compared to the control regimen of brushing followed by a water rinse. In addition, the experimental and marketed mouth rinses did not lower saliva pH compared to the brush/water rinse regimen. All the mouth rinses in this trial were well tolerated and would be considered generally safe when used according to label specifications. This was the first internal trial to evaluate changes in salivary flow and pH for these mouth rinses versus a control. The results show that all the mouth rinses increased salivary flow and didn't lower pH values, which may be useful to oral healthcare practitioners when recommending oral care regimens to control plaque, gingivitis and calculus.

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