JOHNSON & JOHNSON CONSUMER INC.

SUMMARY CLINICAL STUDY REPORT

PROTOCOL TITLE:	A Randomized Clinical Trial to Investigate Two-Week Clinical Safety, Changes in Salivary Flow and pH Following Use of an Anticavity Low-pH Mouthwash
PROTOCOL NUMBER:	CCSORC005342 Final 05 June 2023
SPONSOR:	Johnson & Johnson Consumer Inc. 199 Grandview Road, Skillman, NJ 08558 USA
STUDY SITE:	Salus Research, Inc. 1220 Medical Park Drive, Building 4 Fort Wayne, Indiana 46825 USA
PRINCIPAL INVESTIGATOR:	Jeffery Milleman, DDS, MPA [redacted]
KEY SITE STAFF	Study Director/Designated Physician Representative (DPR): 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):	17 Jul 2023
STUDY COMPLETION DATE (Last Subject Completed):	03 Aug 2023
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.

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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	Previous clinical trials[1,2] have demonstrated the clinical efficacy of both alcohol-containing and alcohol-free mouth rinse formulations containing four essential oils (EOs). These trials also showed a favorable safety profile when these mouth rinses are used according to the label instructions. Nonetheless, additional studies to evaluate the oral soft and hard tissue irritation potential are warranted when new formulations, including the use of new ingredients or new flavors, are developed.
OBJECTIVE	The purpose of this two-week randomized clinical trial was to evaluate the oral soft and hard tissue tolerance of a twice daily regimen of brushing and rinsing with one of three EO-containing mouth rinse formulations versus a brushing only control. The three mouthwash formulations were an experimental anticavity mouthwash that contained alcohol and a unique flavoring ingredient, a marketed mouthwash, and a marketed anticavity mouthwash. In addition, short-term changes in salivary flow and oral pH after a single use of the respective brushing/rinsing regimen were compared to brushing only followed by a water rinse. The primary endpoint was the oral tolerance based on oral hard and soft tissue exams and occurrence of adverse events (AEs). The secondary endpoints were: • The salivary flow rate at baseline (for study inclusion) and then immediately (0) and at 2.5-, 5-, 10-, 15- and 30-minute timepoints. • pH measurements at the 2.5-, 5-, 10-, 15- and 30-minute timepoints. [redacted]
STUDY DESIGN	This examiner-blind, single center, randomized, parallel-group controlled clinical trial study consisted of three site visits over a two-week experimental period. The trial protocol [redacted] provides the complete trial design.
SUBJECT INFORMATION	Subjects were generally healthy adults, at least 18 years of age, in good general and oral health who met the eligibility criteria. The complete eligibility criteria for this study were followed as defined in the study protocol [redacted]

INVESTIGATIONAL STUDY MATERIALS

Identification	UPC/Formula Number	Product Type
LISTERINE ® Clinical Solutions Teeth Strength [redacted] Abbreviated as JE	[redacted]	Investigational Product (IP) (Experimental)
LISTERINE® COOL MINT® ZERO [redacted] Abbreviated as LCMZ	UPC# 312547428323	IP
LISTERINE® TOTAL CARE ZERO [redacted] Abbreviated as LTCZ	UPC# 312547306706	IP
Colgate® Cavity Protection Toothpaste	UPC# 035000510853	Auxiliary Product
Colgate® Full Head/Soft Bristles Toothbrush	UPC# 035000550101	Ancillary Product
Reach® Unflavored Waxed Dental Floss	UPC# 381370092131	Ancillary Product

DOSE AND MODE OF APPLICATION

Subjects were instructed to brush their teeth twice daily for one timed minute using a full ribbon of the assigned toothpaste across the length of the provided soft bristled toothbrush. Subjects assigned to a brush/rinse group were instructed to use the provided dose cups to measure out the appropriate amount of mouthwash to be used. The instructions to subjects in each group were as follows:

- **Brush / Rinse with JE (experimental) –** Brush for one timed minute, then rinse with **10mL** of the assigned full strength mouthwash for **60 seconds** twice a day, morning and night.
- **Brush / Rinse with LCMZ -** Brush for one timed minute, then rinse with **20mL** of the assigned full strength mouthwash for **30 seconds** twice a day, morning and night.
- **Brush / Rinse with LTCZ -** Brush for one timed minute, then rinse with **10mL** of the assigned full strength mouthwash for **60 seconds** twice a day, morning and night.
- **Brush Only –** Brush for one timed minute twice a day, morning and night.

Subjects conducted their assigned oral care regimen (brushing/rinsing or brushing only) for the first time 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.
METHODOLOGY	For each study visit, subjects presented to the clinical site after refraining from oral hygiene for at least four hours, but no more than 12 hours, and refrained from smoking, eating and drinking (including water) for at least one hour prior to the visit. **<u>Visit 1: Day 0 – Screening/Baseline</u>** 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 asked to bring a list of their current medications and supplements and their current toothpaste and mouthwash (if applicable) with them to the site for Visit 1. The site recorded the brand/toothpaste name and how long they have been using that specific brand/toothpaste name, as well as the brand/mouthwash name of mouthwash used (if applicable) and how long they have been using that specific brand/mouthwash name. Next, subjects provided an unstimulated saliva sample after sitting quietly for five minutes. During the timed five-minute saliva collection period, subjects allowed their saliva to pool, emptying it into a collection vial when they felt the need to swallow. During this time, subjects were prohibited from talking, reading and using their cell phones, to avoid distraction from providing the sample. Upon completion, the final amount of saliva was weighed, and flow rate was determined (for study inclusion). The saliva was expressed as mL/min and needed to be 0.3 mL/min or greater for inclusion. Salivary pH of this resting saliva sample was also measured. After the initial saliva collection, subjects had an oral hard and soft tissue assessment and an assessment of other inclusion/exclusion criteria to complete their study qualification. Qualifying subjects were randomly assigned to one of the four study arms in a 2:2:1:1 manner: 1. Brush / Rinse with JE 2. Brush / Rinse with LTCZ 3. Brush / Rinse with LCMZ 4. Brush Only (control group) Subjects were given their study toothbrush, toothpaste, mouthwash (if applicable), floss (if flossing was part of their normal oral hygiene routine), and subject diary/instruction card. Subjects completed their assigned oral care routine at the site under supervision. For the immediate (0) collection timepoint, subjects did the following:

	Subjects in the two groups that rinsed for 60 seconds brushed their teeth with the provided toothpaste for one timed minute, expectorated into a collection tube for 10 seconds, rinsed with their assigned mouthwash according to the product label and then expectorated into the same collection tube for 20 seconds. Subjects in the one group that rinsed for 30 seconds did nothing for 30 seconds, then brushed their teeth with the provided toothpaste for one timed minute, expectorated into a collection tube for 10 seconds, rinsed with their assigned mouthwash according to the product label and then expectorated into the same collection tube for 20 seconds. Subjects in the Brush Only group brushed their teeth with the provided toothpaste for one timed minute, expectorated into a collection tube for 10 seconds, rinsed with 20mL of tap water for 60 seconds and then expectorated into the same collection tube for 20 seconds. Note: For the purpose of the salivary flow and pH assessments, this group rinsed with water following tooth brushing under supervision at the study site. A timed two-minute saliva sample was collected into separate collection vials at the following time points (in minutes): 2.5, 5, 10, 15, and 30. This included a 30-second waiting period prior to brushing for the LCMZ group. The 2.5-minute and 5-minute collection timepoints were 2.5 minutes and 5 minutes after the timer started. The collections at the 10-, 15- and 30-minute timepoints were allowed a ± one-minute window. 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 (the unstimulated resting saliva sample taken for study inclusion before product use) and then at these time points (in minutes): 2.5, 5, 10, 15, and 30. After the saliva samples are collected and weighed, salivary flow rate was calculated, and pH measurements were taken. The baseline and 30-minute sample collection tubes were placed on dry ice and transported within an hour into the -80C freezer for storage, then were shipped on dry ice to the Sponsor at the end of Visit 1 [redacted]. All other saliva samples were destroyed by the site after the weight, salivary flow rate and pH measurements were taken. Documentation of the destruction was provided to the Sponsor. AEs were collected, and the next visit was scheduled.

	Visit 2 (Day 3 ± 1 day) and **Visit 3 (Week 2 ± 1 day)** At both visits, hard and soft tissue tolerance was evaluated. Compliance was evaluated by weighing residual volumes of returned mouthwash (if applicable), visually inspecting toothpaste tubes to ensure proper use and by reviewing the subject diary cards. AEs were collected. At Visit 2, the next visit was scheduled. At Visit 3, female subjects of childbearing potential were given a urine pregnancy test. At the end of Visit 3, subjects were dismissed from the trial. --- 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 emergency treatment. --- Statistical Analysis: Safety analysis including oral hard and soft tissue exams and AEs was based on the Safety Analysis Set. The number and percentage of subjects with treatment-emergent AEs (TEAEs) 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 in the study was presented by visit and by investigational product. The analysis of salivary flow rate and pH measurement was based on the Full Analysis Set. Pairwise comparisons between investigational products were 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 also included to compare investigational products at specific timepoints. The within subject correlation structure was specified as unstructured. It should be noted that after the completion of the trial, review of the data showed that the baseline pH measurements for all subjects were outside of what is regarded to be normal salivary pH measurements. To investigate further, it was decided to re-run this part of the study as a separate randomized clinical trial to evaluate pH changes after a single use of the three interventional products. Results of that trial will be reported in a future Clinical Study Report. [redacted]
MEASUREMENT AND/OR EVALUATION SCHEDULE	Saliva sampling and salivary pH was conducted only at Visit 1 (Baseline). Assessment of oral tissue tolerance occurred at every visit through oral exams and the collection of AEs.

INSTITUTIONAL REVIEW BOARD (IRB)	This study was reviewed and approved by the following IRB: - Veritas IRB Inc. - +1 (866) 384-4221 - info@veritasirb.com - Approval date: 06 Jun 2023
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 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 adverse events 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 oral tissue tolerance of an experimental mouth rinse containing essential oils, alcohol and an anticaries ingredient (fluoride) used as directed in a twice daily oral hygiene regimen was similar to the oral tissue tolerance seen in a twice daily brushing only regimen. Although not directly compared, the experimental mouth rinse had a lower percentage of AEs than the two marketed essential oil-containing, alcohol-free mouth rinses. Following a single use of brushing and rinsing, the three mouth rinses increased salivary flow and pH up to 30 minutes after use. All the mouth rinses in this trial were well tolerated and would be considered generally safe when used according to label specifications.

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