JOHNSON & JOHNSON CONSUMER INC.

SUMMARY CLINICAL STUDY REPORT

PROTOCOL TITLE:	Twelve Week Safety and Clinical Efficacy of Experimental Mouth Rinses
PROTOCOL NUMBER:	CCSORC002549 Amendment 1 _ 18 March 2021
SITE STUDY NUMBER:	1001
SPONSOR:	Johnson & Johnson Consumer Inc. [redacted]
STUDY SITE:	All Sum Research Center Ltd. 6635 Kitimat Road, Units 36 & 37 Mississauga, Ontario L5N 6J2 CANADA
PRINCIPAL INVESTIGATOR:	Dr. Chhaju Ram Goyal Address: refer to study site address [redacted]
KEY STUDY STAFF:	Study Director and Designated Physician Representative: Mary Lynn Bosma, RDH, DDS [redacted] Study Manager: Alicia DelSasso, CCRP, [redacted]
STUDY INITIATION DATE (First Subject First Visit):	29-MAR-2021
STUDY COMPLETION DATE (Last Subject Completed):	23-JUL-2021
SITE APPROVAL:	[redacted]
SPONSOR REVIEW AND APPROVAL:	

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	Listerine mouth rinse formulations contain four essential oils (EOs): menthol (mint), thymol (thyme), methyl salicylate (wintergreen) and eucalyptol (eucalyptus). It has been well documented that these four essential oils are effective in the reduction of plaque and gingivitis[1]. This study evaluated the safety and efficacy of three experimental (prototype) mouth rinse formulations [redacted] compared to a positive control, Listerine Cool Mint (LCM) [redacted] and a hydroalcohol negative control (NC) [redacted] for the prevention and reduction of gingivitis and plaque as an adjunct to tooth brushing when used twice daily as directed during a 12-week treatment period. [redacted]
OBJECTIVES	The purpose of this study was to evaluate the safety and efficacy of three experimental (prototype) mouth rinse formulations compared to a hydroalcohol negative control mouth rinse and a positive control mouth rinse for the reduction of gingivitis and plaque when used as an adjunct to tooth brushing during a 12-week product usage period.
STUDY DESIGN	The study protocol referenced on page 20 of this report provides the complete study design for the study. In brief, this examiner-blind, single center, randomized, parallel-group controlled clinical trial study consisted of a 12-week experimental period, with five site visits.
SUBJECT INFORMATION	The complete eligibility criteria for this study were followed as defined in the study protocol referenced on page 20 of this report. Generally healthy adult subjects 18 to 60 years of age, in good general and oral health who met the eligibility criteria entered the study. Among other criteria, subjects had at least 20 natural teeth with scorable surfaces. At Baseline, subjects must have had a mean Modified Gingival Index (MGI) and a mean Turesky Plaque Index (TPI) of $\geq$ 1.95 and an Expanded Bleeding Index (EBI) of $\geq$ 10%.

INVESTIGATIONAL STUDY MATERIALS	<table><tr><th>Identification</th><th>Formula number</th><th>Product type</th></tr><tr><td>Hydroalcohol [redacted]</td><td>[redacted]</td><td>Negative control</td></tr><tr><td>Hydroalcohol Prototype [redacted]</td><td>[redacted]</td><td>Investigational Product (IP)</td></tr><tr><td>Avant Prototype [redacted]</td><td>[redacted]</td><td>IP</td></tr><tr><td>Zero Prototype [redacted]</td><td>[redacted]</td><td>IP</td></tr><tr><td>LISTERINE® COOL MINT® Antiseptic Mouthwash [redacted]</td><td>[redacted]</td><td>Positive control</td></tr></table> Brushing with Colgate® Cavity Protection toothpaste [redacted] and an ADA-approved toothbrush (ID# 751795) was done by subjects before rinsing in all groups. All mouth rinses were used after brushing.
DOSE AND MODE OF APPLICATION	Subjects were instructed to brush their teeth twice daily (morning and evening) in their usual manner with the toothpaste and soft bristled toothbrush provided. Following each brushing, subjects rinsed with 20mL of their assigned mouth rinse for 30 timed seconds, twice a day following brushing.
METHODOLOGY	Three hundred generally healthy subjects who met the required inclusion/exclusion criteria at the Screening visit were enrolled in this study. Subjects were randomized among the 5 treatment groups in a 2:2:2:2:1 allocation ratio, with the "1" representing the negative control group. This examiner-blind, single center, randomized, parallel-group controlled clinical trial study consisted of a 12-week experimental period. The Screening visit was permitted to occur up to 14 days prior to the Baseline visit. In addition, Baseline and Screening were permitted to be a combined visit. **Visit 1: Screening** At Visit 1, subjects were consented and had their prior and concomitant medications/non-drug therapies, smoking, significant medical and dental histories recorded and inclusion and exclusion criteria reviewed. Qualified study examiners conducted oral examinations and assessment of hard and soft tissues for all subjects. Periodontal pocket depth on all teeth was checked for study entry.

	For Visits 2 through 5: All subjects presented to the clinical site after refraining from oral hygiene for at least 8 hours (but no more than 18 hours) and refraining from eating for at least 4 hours prior to the visit (water was allowed up to 2 hours prior to examinations). The examinations were performed in the following order: oral examination, MGI, EBI and TPI. For each examination index, the same examiner was responsible for that index throughout the study. Throughout the study, subjects were permitted to continue to use an interdental cleaning device to remove impacted food between the teeth if it was part of their usual oral care regimen. 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. **Visit 2: Day 0 – Baseline** Female subjects of childbearing potential were given a urine pregnancy test. For all subjects, study personnel reviewed inclusion/exclusion criteria, queried for Adverse Events (AEs) and concomitant medications/non-drug therapies to ensure subjects were still eligible to participate in the study since their screening visit. Qualified study examiners conducted oral examinations and assessment of hard and soft tissues, followed by assessment of gingivitis (MGI), bleeding (EBI) and plaque (TPI). Each subject received a complete dental prophylaxis performed by a qualified dental professional. The teeth were checked by another qualified professional to ensure completeness of prophylaxis. Subjects were randomly assigned to one of five treatment groups. Subjects received their assigned mouth rinse product, dose cups, and a diary card/subject instruction sheet. Subjects began using their assigned study products following the label instructions. Subjects were instructed to brush twice daily in their usual manner with a marketed fluoride-containing dentifrice (Colgate® Cavity Protection Toothpaste) and a marketed soft bristled toothbrush. The toothpaste and toothbrushes were supplied to the subjects at this visit to use throughout the study. The first product use (brushing and rinsing) was conducted at the site under supervision of study personnel. Subjects were asked if they experienced any adverse events after their first product use. All other brushing and rinsing were unsupervised. Subjects were instructed to record completion of twice daily brushing and rinsing on the subject diary card.

	Visit 3: Day 7 – 1 Week Post Baseline (± 1 day) *and* **Visit 4: Day 28 – 4 Weeks Post Baseline (± 2 days)** Subjects brought all their mouth rinse bottles (empty and full), study toothbrush and toothpaste with them. Study personnel assessed usage compliance by visually inspecting toothpaste for use, weighing mouth rinse bottles, reviewing diary cards and if necessary, reinforcing the usage directions. Empty bottles were kept by the study site, other study products were returned to the subjects. At Visit 4, assigned mouth rinses were replenished and subjects received new diary cards. Study personnel reviewed inclusion/exclusion criteria, queried for AEs and concomitant medications/non-drug therapies to ensure subjects were still eligible to participate in the study. Qualified study examiners conducted oral examinations and assessment of hard and soft tissues, followed by assessment of gingivitis (MGI), bleeding (EBI) and plaque (TPI). **Visit 5: Day 84 – 12 Weeks Post Baseline (± 3 days)** Subjects brought all their mouth rinse bottles (empty and full), study toothbrush and toothpaste with them. Study personnel collected all mouth rinse bottles and toothpaste and assessed usage compliance by visually inspecting toothpaste for use, weighing mouth rinse bottles and reviewing diary cards. Study personnel reviewed inclusion/exclusion criteria, queried for AEs and concomitant medications/non-drug therapies to ensure subjects were still eligible to participate in the study. Female subjects of childbearing potential were given a urine pregnancy test. Qualified study examiners conducted oral examinations and assessment of hard and soft tissues, followed by assessment of gingivitis (MGI), bleeding (EBI) and plaque (TPI). Study subjects were dismissed at the conclusion of this visit.
MEASUREMENT AND/OR EVALUATION SCHEDULE	Measurements included the Turesky Modification of the Quigley-Hein Plaque Index (TPI), the Modified Gingival Index (MGI) and the Expanded Gingival Bleeding Index (EBI). All assessments were conducted at Visits 2 (Baseline), 3 (Week 1), 4 (Week 4) and 5 (Week 12). Comparisons between IPs were based on a mixed-effects repeated measures analysis, including terms for investigational product and visit, and the baseline value as a covariate. Superiority tests were performed comparing each prototype [redacted]

	mouth rinse with the NC mouth rinse, and LCM with the NC mouth rinse. For each prototype mouth rinse that was statistically significantly better than NC for both mean MGI and mean TPI at 12 weeks, non-inferiority tests at 12 weeks were performed versus LCM. For a prototype [redacted] mouth rinse, non-inferiority versus LCM was concluded with respect to an endpoint if the mean for that prototype mouth rinse was statistically significantly lower than the average of the means for LCM and NC. To further assess the effects of the prototype [redacted] mouth rinse versus the effects of LCM, Fieller's method was used to construct 95% confidence intervals. Each superiority test was carried out at the 0.05 level of significance, two-sided. Non-inferiority testing was performed at the (one-sided) 0.025 level of significance. Considering the sequential nature of testing for hypotheses involving a specific prototype rinse, the familywise error rate was controlled at 0.05 for each family of hypotheses involving a specific prototype rinse for each primary endpoint. The same models were applied to the secondary and exploratory endpoints, except for the non-inferiority tests, which were only conducted on primary endpoints. See the protocol for more details. **Primary:** The primary efficacy variables were whole mouth mean MGI and whole mouth mean TPI after 12 weeks of product use. **Secondary:** The secondary efficacy variables were the whole mouth mean TPI after one and four weeks of product use, the whole mouth mean MGI after four weeks, and whole mouth mean EBI and percent bleeding sites, based on the Expanded Gingival Bleeding Index at four and 12 weeks. [redacted] Safety assessments included oral tissue tolerance, monitored through oral exams and the collection of adverse events, and oral hard and soft tissue assessments. 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 adverse

	events. Details of adverse events including resolution were captured.
INSTITUTIONAL REVIEW BOARD (IRB)/INDEPENDENT ETHICS COMMITTEE (IEC) INFORMATION	This study was reviewed and approved by the following IRB/IEC: - Name: Veritas IRB - Approval date: 27 Jan 2021
SAFETY AND ADVERSE EVENTS	All AEs and Serious AEs (SAEs) were collected regardless of causal relationship to the subject's participation in the study. The information was collected/reported within the reporting timelines specified in the protocol.
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, to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities.
CONCLUSIONS	The results of this study show that mouth rinse formulations [redacted] reduced plaque, gingivitis, gingival bleeding and percent bleeding sites better than a hydroalcohol negative control rinse [redacted] after 12 weeks of use. Furthermore, these significant reductions in plaque, gingivitis, gingival bleeding and percent bleeding sites for the three prototypes and the positive control versus negative control were seen as early as four weeks of product use. In addition, non-inferiority tests to compare LCM to the three study prototypes showed that the hydroalcohol and Zero prototypes were non-inferior with respect to plaque and gingivitis reduction compared to LCM. The Avant prototype demonstrated non-inferiority compared to LCM for gingivitis reduction, but not for plaque reduction. In this study, the composition of the Avant prototype may have lessened the optimal effect [redacted] and will be investigated further. All the study rinses were well tolerated with only two instances of mild oral mucosal exfoliation in one of the prototypes.

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