JOHNSON & JOHNSON CONSUMER INC.

SUMMARY CLINICAL STUDY REPORT

PROTOCOL TITLE:	Six Week Safety and Clinical Efficacy of Experimental Mouth Rinses: Effect on Gingivitis and Plaque
PROTOCOL NUMBER:	CCSORC001793 Amendment 2, dated 18 September 2019
SITE STUDY NUMBER	1001
SPONSOR:	Johnson & Johnson Consumer Inc. [redacted]
STUDY SITE:	Salus Research, Inc. 1220 Medical Park Drive, Building #4 Fort Wayne, IN 46825 [redacted]
PRINCIPAL INVESTIGATOR:	Jeffery Milleman, DDS, MPA Address: Refer to Study Site address [redacted]
KEY SITE STAFF	Sub-Investigator: Kimberly R. Milleman, RDH, BSEd, MS [redacted] Study Director/Designated Physician Representative (DPR): Mary Lynn Bosma, RDH, DDS Director Oral Health, Medical Affairs and Clinical Research [redacted]
STUDY INITIATION DATE (First Subject First Visit):	08 October 2019
STUDY COMPLETION DATE (Last Subject Completed):	19 December 2019

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	Plaque induced gingivitis is a reversible inflammation of the gingiva caused by biofilm bacteria at the gingival margin. Consistent daily plaque control to manage this biofilm is necessary to achieve gingival health and it is highly desirable to have products that help to maintain the healthy state. Over and above regular homecare of brushing with an ordinary dentifrice, antimicrobial mouth rinse (such as LISTERINE®) has been recommended by various professional agencies (the American Dental Association) to help control plaque and gingivitis. Clinical gingival health is identified by minimal sulcus depth, stippling, gingival color of pale or coral pink with a knife edge that adapts closely around the tooth with no evidence of bleeding when probed. Clinical gingivitis, however, is identified by erythema and edema of the gingiva often accompanied by bleeding of the gingival margin when stimulated.
OBJECTIVES	The objective of this study was to evaluate the safety and efficacy of experimental mouth rinse formulations with a unique flavor compared to a Positive control mouth rinse and a hydroalcohol control mouth rinse for the reduction of gingivitis and plaque when used as an adjunct to tooth brushing during a six-week product usage period. **Primary:** The primary efficacy variables were whole mouth mean modified gingival index (MGI) (mean MGI) and whole mouth mean plaque index (PI) (mean PI) after six weeks of product use. **Secondary:** The secondary efficacy variables were the whole mouth mean PI after four weeks of product use, the whole mouth mean MGI after four weeks, whole mouth mean expanded bleeding index(EBI) (mean EBI) and percent bleeding sites, based on the expanded gingival bleeding Index at four and six weeks. [redacted]
STUDY DESIGN	This was an examiner-blind, single-center, randomized, parallel-group controlled clinical study consisting of a six-week experimental period. The study protocol referenced on page 52 of this report provides the complete study design for the study.
SUBJECT INFORMATION	The complete eligibility criteria for this study were followed as defined in the study protocol referenced on page 52 of this report. The main inclusion criteria included subjects ≥18 years of age in good general and oral health without any known allergy to commercial dental products or cosmetics; with minimum of 20 gradable teeth including 4 molars with scorable facial and lingual surfaces; with a baseline mean gingival index ≥1.95 for subjects in the randomized treatment group and ≤0.75 for subjects in the healthy reference group per the MGI; with a mean PI ≥1.95 for subjects in the randomized treatment group per the 6 site Turesky modification of the Quigley-Hein Plaque Index at Baseline; ≥10% bleeding sites for subjects in the randomized treatment group, and ≤3% bleeding sites for subjects in the healthy reference group at

	Baseline; absence of significant oral soft tissue pathology and moderate/advanced periodontitis (based on a visual/clinical examination and at the discretion of the dental examiner); and absence of fixed or removable orthodontic appliance or removable partial dentures. Female subjects of child-bearing potential were included if they had negative pregnancy urine tests.
INVESTIGATIONAL STUDY MATERIALS	<table><tr><th>Identification</th><th>Formula/UPC Number</th><th>Product Type</th></tr><tr><td>[redacted] (Prototype 1)</td><td>[redacted]</td><td>Experimental</td></tr><tr><td>[redacted] (Prototype 2)</td><td>[redacted]</td><td>Experimental</td></tr><tr><td>5% Hydroalcohol mouthrinse (Negative control)</td><td>[redacted]</td><td>Negative Control</td></tr><tr><td>LISTERINE® COOL MINT® (Positive control)</td><td>[redacted]</td><td>Positive Control</td></tr><tr><td>COLGATE® CAVITY PROTECTION TOOTHPASTE</td><td>[redacted]</td><td>Auxiliary Product</td></tr><tr><td>Concept Curve Winter Series Toothbrush</td><td>[redacted]</td><td>Ancillary Product</td></tr></table>
DOSE AND MODE OF APPLICATION	The subjects were randomized to one of the 4 treatment groups (mouth rinses) as below: • Negative Control Mouthrinse: 5% hydroalcohol mouthrinse • Positive Control Mouthrinse: LISTERINE® COOL MINT® • Prototype 1 [redacted] • Prototype 2 [redacted] Mouth rinse: After brushing, rinse for 30 seconds with 20 mL of assigned mouth rinse (morning and evening). Toothpaste: Brush twice daily in usual manner (morning and evening) with the toothpaste and soft bristled toothbrush provided. Placed a full ribbon of toothpaste across the length of the toothbrush.
METHODOLOGY	One hundred twenty-five (125) subjects that met the required inclusion/exclusion criteria at the Screening/Baseline visit were enrolled for treatment in this study (referred to as the randomized treatment group). An additional 32 subjects who are identified as healthy by the defined criteria were a comparison group [redacted] (referred to as the healthy reference group). This was an examiner-blind, single-center, randomized, parallel-group controlled clinical study which consisted of a six-week experimental period.

[redacted]

Visit 1: Day 0 – Screening/Baseline (Healthy Reference Group and Randomized Treatment Groups)

At Visit 1, subjects presented to the clinical site having refrained from oral hygiene for at least 8 hours, but no more than 18 hours, and refrained from eating and smoking for at least 4 hours prior to oral examination (water was allowed up to 2 hours prior to examinations). Subjects were consented, had their prior and concomitant medications/non-drug therapies, smoking, significant medical and dental histories, and inclusion and exclusion criteria were reviewed. [redacted]

Female subjects of child-bearing potential were given a urine pregnancy test (healthy reference and randomized treatment groups).

[redacted]

For subjects who were in the healthy reference group, (teeth numbers 3, 7, 18, and 23) gingiva must have had sample site MGI scores of 0 or 1 and no bleeding, whole mouth mean MGI ≤0.75, whole mouth bleeding sites less than or equal to 3%, and pocket depth was less than or equal to 3 mm.

For subjects who were in the Randomized Treatment Groups, the same four teeth (3, 7, 18, and 23) were the preferred teeth [redacted] but must have had a sample site MGI score of ≥2 and had at least one bleeding site on the sampled tooth, and less than or equal to 4 mm. Subjects had a whole mouth mean MGI ≥1.95 at Baseline and whole mouth bleeding sites greater than or equal to 10%. [redacted]

Other inclusion/exclusion criteria for entry into the study at the Screening/Baseline visit, include examinations of the oral tissues (oral hard and soft tissue assessment), periodontal pocket depth (were checked for all teeth for entry), gingivitis (MGI), bleeding of 168 sites (EBI), and plaque assessments (PI), completed baseline oral examinations.

The healthy reference group [redacted] was screened and enrolled at a separate examination. They participated in the examinations [redacted] and did not receive a prophylaxis or product. The study was completed for that group.

For the randomized treatment group, a complete dental prophylaxis was 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 four Randomized Treatment Groups. They received their assigned mouth rinse product, dose cups, soft bristled toothbrush, and marketed toothpaste (COLGATE® CAVITY PROTECTION TOOTHPASTE), timers (if needed), and a diary card/subject instruction to record their twice daily brushing and rinsing times.

[redacted]

	Subjects began the use of their assigned study products following the label instructions. The first product used (brushing and rinsing) was conducted at the site under supervision of study personnel. Subjects were asked if they experienced any AE after their first product use. All other brushing and rinsing were unsupervised. Subjects were instructed to brush twice daily in their usual manner and to use their mouth rinse according to the directions on the label. Oral tissue tolerance, MGI, EBI and PI were assessed. [redacted] **Visit 2: Day 7 – 7 Days Post Baseline (± 1 day)** Subjects were to visit the clinical site for similar examinations at Visit 1. An oral examination (oral hard and soft tissue assessment) was performed [redacted] **Visit 3 Day 28 – 4 Weeks Post Baseline (± 2 days)** Subjects were to visit the clinical site for similar examinations at Visit 1. The site assessed compliance with use of the investigational products (IPs) by means of visually inspecting toothpaste for use, weighing mouth rinse bottles, reviewing diary cards and if necessary, reinforce the usage directions. Subjects received an oral examination/assessment (oral hard and soft tissue assessment, gingivitis, bleeding, and plaque assessments). A new diary card/subject instruction was given. Adverse events (AEs) were assessed. Oral tissue tolerance, MGI, EBI and PI were assessed. [redacted] **Visit 4: Day 42 – 6 Weeks Post Baseline (± 3 days) (endpoint)** Subjects were to visit the clinical site for similar examinations at Visit 1. The site assessed compliance with use of the IPs by means of visually inspecting toothpaste for use, weighing mouth rinse bottles and reviewing diary cards. Inclusion/exclusion criteria, AE assessment and concomitant medications/non-drug therapies were reviewed to ensure subjects were still eligible to participated in the study. Female subjects of child-bearing potential were given a urine pregnancy test. Subjects were given an oral examination/assessment (oral hard and soft tissue assessment, gingivitis, bleeding, and plaque assessments). Subjects recorded all brushing and rinse times on their subject diary card. [redacted] AEs were assessed.

[redacted]

Oral tissue tolerance, MGI, EBI and PI were assessed. [redacted]

Oral tissue tolerance was monitored through an oral exam at every visit. The collection and assessment of AEs were performed at each visit. [redacted]

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.

Statistical Analysis

Sample size determination: A sample size of 30 completed subjects per group provided 80% power to detect a standardized effect size (difference between treatment population means divided by population standard deviation [SD]) of 0.75. This calculation was based on a two-sided test at the 5% significance level. The standardized effect size was based on two previous studies that included 4 to 6 weeks data.

Assuming a 5% dropout rate, 125 subjects in total were randomized to ensure the 120 subjects completed the study for the randomized treatment group.

Baseline and demographics: Baseline and demographic characteristics were presented overall and by IP group. Demographic and baseline characteristics were compared across IP groups using analysis of variance (ANOVA) or a Chi-Square test (as appropriate for the type of data being considered). If the expected number of subjects within a specific category was sufficiently small, Fisher's exact test was used in the place of the Chi-Square test.

The Healthy Reference Group subjects were summarized separately in one group at Screening/Baseline visit.

Efficacy Analyses: Efficacy analysis was based on Full Analysis Set, defined as all subjects who had baseline and post-baseline efficacy data.

Endpoints:

The primary efficacy endpoints were the whole mouth mean MGI and whole mouth mean PI after six weeks of product use. The secondary endpoints were whole mouth mean PI after four weeks, whole mouth mean MGI after four weeks, whole mouth mean EBI after 4 and 6 weeks, and percent of bleeding sites, based on the expanded gingival bleeding index after four and six weeks. [redacted]

For primary and secondary endpoints, between-treatment comparisons which were based on a mixed model for repeated measures (MMRM) (including all post baseline visits), including terms for treatment and visit, and the corresponding baseline value as a covariate. Treatment-by-visit and baseline by-visit terms were included, to perform the comparisons at specific visits.

Superiority tests were performed which compared each Prototype mouth rinse with the Negative and Positive control mouth rinse, and the Positive control versus Negative control as well. Differences between treatment means and between group comparison were estimated based on this model.

The following between-treatment comparisons were performed; p-values, standard errors, and corresponding 95% confidence intervals were provided:

- LISTERINE® COOL MINT® (Positive control) vs 5% Hydroalcohol (Negative control)
- [redacted] Prototype 1 [redacted] vs 5% Hydroalcohol (Negative control)
- [redacted] Prototype 2 [redacted] vs 5% Hydroalcohol (Negative control)
- [redacted] Prototype 1 [redacted] vs LISTERINE® COOL MINT® (Positive control)
- [redacted] Prototype 2 [redacted] vs LISTERINE® COOL MINT® (Positive control)

Each statistical test was carried out at the 0.05 level of significance, two-sided. No multiple comparison adjustment was made.

[redacted]

	[redacted] Safety Analyses: The safety analysis was based on the safety analysis set. The safety analysis set was defined as all subjects who are randomized and use IP. The number and percentage of subjects experiencing AEs and those experiencing treatment-related AEs were tabulated by Medical Dictionary for Regulatory Activities System Organ Class, preferred term, and IP. Treatment-related AEs included events marked as being possibly, probably, or very likely related to study product. A summary tabulation of conditions and irritation scores by anatomical site based on the oral examinations in the study, was presented.
MEASUREMENT AND/OR EVALUATION SCHEDULE	**Efficacy Evaluations:** One (1) trained calibrated dental examiner performed clinical examinations based on safety and efficacy in a blinded manner. The blinded examiner performed the examinations/assessments in the following order: OST, MGI (if applicable), bleeding index (if applicable), pocket depth (visit 1 only), [redacted] and PI (if applicable). Each subject was examined by this same examiner throughout the course of the study. For each MGI, bleeding index, and PI scoring assessment, the examiner called out his/her findings to the recorder who entered the findings directly into the electronic data capture (EDC) system.

Modified Gingival Index (MGI)

Gingivitis was assessed at all visits by the MGI on the buccal and lingual marginal gingivae and interdental papillae of all scorable teeth:

0=Normal (absence of inflammation)
1=Mild inflammation (slight change in color, little change in texture) of any portion of the entire gingival unit
2=Mild inflammation of the entire gingival unit
3=Moderate inflammation (moderate glazing, redness, edema, and/or hypertrophy) of the gingival unit.
4=Severe inflammation (marked redness and edema/hypertrophy, spontaneous bleeding, or ulceration) of the gingival unit.

Expanded Gingival Bleeding Index (EBI)

Bleeding was assessed at all visits according to the expanded gingival bleeding index, 168 Sites. A periodontal probe with a 0.5 mm diameter tip was inserted into the gingival crevice and swept from distal to mesial around the tooth at an angle of approximately 60°, while in contact with the sulcular epithelium. Each of 6 gingival areas (distobuccal, mid-buccal, mesiobuccal, distolingual, mid-lingual, and mesiolingual) around each tooth will be assessed. After approximately 30 seconds, bleeding at each gingival unit was recorded according to the following scale:

0=Absence of bleeding after 30 seconds
1=Bleeding after 30 seconds
2=Immediate bleeding

Turesky Modification of the Quigley Hein Plaque Index (PI)

Plaque area was scored at all visits by the Turesky modification of the Quigley-Hein Plaque Index, on 6 surfaces (distobuccal, midbuccal and mesiobuccal, distolingual, midlingual and mesiolingual) of all scorable teeth, following disclosing:

0=No Plaque
1=Separate flecks or discontinuous band of plaque around the gingival (cervical) margin
2=Thin (up to 1 mm), continuous band of plaque at the gingival margin
3=Band of plaque wider than 1 mm but less than 1/3 of the surface
4=Plaque covering 1/3 or more, but less than 2/3 of the surface
5=Plaque covering 2/3 or more of the surface

[redacted]

[redacted]

	[redacted] **Safety Assessment** An oral examination was conducted at all exam visits to monitor oral soft and hard tissues tolerance to the treatments. Buccal and sublingual mucosae, lips/labial mucosa, mucobuccal fold, gingiva, tongue, hard and soft palate, uvula, oropharynx, teeth, and dental restorations were examined and findings were recorded in the EDC system. Changes from the baseline were recorded. Clinically significant findings were recorded as AEs in the EDC system. Progress notes for additional AE information not captured in EDC were captured separately in subject source document. The Investigator assessed the relationship toIP. An expected outcome for some subjects was a mild, brief burning or tingling/cooling and minty sensation or mild peeling of the oral soft tissues. If there was no clinical aberration in those subjects reporting this sensation, then it was not considered an AE. All other oral complaints requiring a clinical evaluation and diagnosis were recorded as an AE.
INSTITUTIONAL REVIEW BOARD (IRB)/INDEPENDENT ETHICS COMMITTEE (IEC) INFORMATION	This study was reviewed and approved by the following IRB/IEC: - Name: IntegReview IRB - Approval date: 20 September 2019 Applicable Amendments: Protocol Amendment 2, 18 September 2019

<table>
<tr><td></td><td>- Approval date: 02 October 2019</td></tr>
<tr><td>SAFETY AND ADVERSE EVENTS</td><td>All AEs/serious adverse events (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.</td></tr>
<tr><td>MONITORING, QUALITY CONTROL, AND QUALITY ASSURANCE</td><td>The study monitoring was conducted as per the Sponsor´s requirements. The Study Site was subjected to review by the IRB to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities.</td></tr>
<tr><td>CONCLUSIONS</td><td>

After 6 weeks of product use, mean MGI and PI results showed that compared with Negative control, superiority (p<0.001) was demonstrated for Prototype 1 and Prototype 2. In addition, results from mean MGI showed that Prototype 1 and Prototype 2 were not statistically significantly different from the Positive control. Mean PI results showed that, Prototype 1 versus Positive control was not significantly different. However, the mean for Prototype 2 was significantly higher than the mean for the Positive control (p<0.001).
The overall conclusions for primary and secondary efficacy endpoints are displayed in below table:

<table>
<tr><th></th><th></th><th></th><th>Negative Control (N=31)</th><th>Prototype1 (N=29)</th><th>Prototype2 (N=30)</th><th>Positive Control (N=31)</th></tr>
<tr><td rowspan="3">Mean Plaque Index</td><td>BL</td><td>Mean</td><td>2.98</td><td>3.01</td><td>2.90</td><td>3.11</td></tr>
<tr><td>Wk4</td><td>LS Mean (percent difference)</td><td>2.64</td><td>2.04 (-22.6%)*</td><td>2.48 (-5 9%)#</td><td>1.99 (-24.7%)*</td></tr>
<tr><td>Wk6</td><td>LS Mean (percent difference)</td><td>2.99</td><td>2.17 (-27.3%)*</td><td>2.57 (-14.0%)*#</td><td>2.21 (-26.2%)*</td></tr>
<tr><td rowspan="3">Mean Modified Gingival Index</td><td>BL</td><td>Mean</td><td>2.51</td><td>2.58</td><td>2.42</td><td>2.61</td></tr>
<tr><td>Wk4</td><td>LS Mean (percent difference)</td><td>1.89</td><td>1.76 (-6.9%)#</td><td>1.65 (-12.5%)*#</td><td>1.42 (-24.6%)*</td></tr>
<tr><td>Wk6</td><td>LS Mean (percent difference)</td><td>2.07</td><td>1.29 (-37.4%)*</td><td>1.23 (-40.6%)*</td><td>1.15 (-44.4%)*</td></tr>
<tr><td rowspan="3">Mean Expanded Bleeding Index</td><td>BL</td><td>Mean</td><td>0.34</td><td>0.36</td><td>0.35</td><td>0.38</td></tr>
<tr><td>Wk4</td><td>LS Mean (percent difference)</td><td>0.29</td><td>0.27 (-6.8%)</td><td>0.27 (-6.8%)</td><td>0.25 (-14.1%)</td></tr>
<tr><td>Wk6</td><td>LS Mean (percent difference)</td><td>0.36</td><td>0.23 (-36.3%)*</td><td>0.22 (-40.0%)*</td><td>0.22 (-38.0%)*</td></tr>
<tr><td rowspan="3">Percent Bleeding sites</td><td>BL</td><td>Mean</td><td>24.0%</td><td>25.9%</td><td>24.9%</td><td>26.7%</td></tr>
<tr><td>Wk4</td><td>LS Mean (percent difference)</td><td>20.1%</td><td>18.4% (-8.9%)</td><td>19.3% (-4.4%)</td><td>17.4% (-13.6%)</td></tr>
<tr><td>Wk6</td><td>LS Mean (percent difference)</td><td>27.5%</td><td>15.6% (-43.1%)*</td><td>15.6% (-43.1%)*</td><td>16.4% (-40.2%)*</td></tr>
</table>
BL: Baseline, Wk4: Week 4, Wk6: Week 6
*Statistically significantly different from 5% hydroalcohol mouthrinse (negative control), p<0.05
#Statistically significantly different from Listerine Cool mint, p<0.05
Percent difference is for comparison vs Negative control
Negative Control: 5% Hydroalcohol mouthrinse.
Prototype1[redacted]
</td></tr>
</table>

	Prototype Z Positive Control: Listerine® Cool Mint®. • [redacted] • All study treatments were well tolerated in this study.