Summary Clinical Study Report, Version *1* –Approved – dated 09 March 2020
Protocol Number: CCSORC000708
Site Study Number: 1001

JOHNSON & JOHNSON CONSUMER INC.

SUMMARY CLINICAL STUDY REPORT

PROTOCOL TITLE:	Pilot Study: Twelve Week Clinical Efficacy of Supervised Mouth Rinse and Flossing: Effect on Plaque and Gingivitis
PROTOCOL NUMBER:	CCSORC000708 Version 1.0 dated *09 Aug 2018*
SITE STUDY NUMBER	1001
SPONSOR:	Johnson & Johnson Consumer Inc. [redacted]
STUDY SITE:	Salus Research, Inc [redacted] Fort Wayne, IN 46825 USA
PRINCIPAL INVESTIGATOR:	[redacted]
KEY SITE STAFF	[redacted]
STUDY INITIATION DATE (First Subject First Visit):	26-SEP-2018
STUDY COMPLETION DATE (Last Subject Completed):	21-DEC-2018
SITE APPROVAL:	

Name	Signature and date:
[redacted]	

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SPONSOR REVIEW AND APPROVAL:	**Name**	**Signature and date:**
	[redacted]	

The principles of the International Council for Harmonization (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 Harmonization (ICH) (GCP E6 [R2]) were applied to this study.

INTRODUCTION	Bacterial plaque is an important factor in dental diseases such as caries and gingivitis. Plaque control methods include a variety of products. Mechanical methods included both brushing and flossing; however, most individuals have difficulty in maintaining oral hygiene standards and mastering mechanical plaque control as these methods are dependent on dexterity.[2] Two controlled studies have been published relating to the relative efficacy of an essential oils containing mouth rinse versus dental flossing in the ability to control the accumulation of plaque and subsequently the prevention/reduction of gingivitis.[1,3] One of these studies indicated that rinsing twice daily with an essential oil mouth rinse was at least as good as unsupervised daily flossing in reducing interproximal plaque and gingivitis. The second study indicated that the essential oil mouth rinse was as good as floss in controlling interproximal gingivitis. This new study investigated the effects of optimal flossing by either a hygienist or self-flossing by a subject under supervision in comparison to twice daily rinsing with an essential oil mouth rinse or a hydroalcohol control rinse.
OBJECTIVES	**Objectives:** To evaluate the efficacy of twice daily alcohol containing Essential Oil mouth rinse and brushing versus dental flossing and brushing under once daily supervision for the prevention and reduction of plaque and gingivitis. **Primary**: The primary efficacy variable was interproximal mean Turesky Modification of the Quigley-Hein Plaque Index (TPI) and interproximal mean Modified Gingival Index (MGI) after 12 weeks of product use. **Secondary**: The secondary efficacy variables were the interproximal mean TPI after four weeks of product use, the interproximal mean MGI after four weeks, whole-mouth mean TPI after 4 and 12 weeks, whole-mouth mean MGI after 4 and 12 weeks, whole-mouth and interproximal mean Bleeding Index (BI) after 4 and 12 weeks, whole-mouth and interproximal percent bleeding sites at 4 and 12 weeks based on the BI, and the interproximal of the Proximal Marginal Plaque Index (PMI). [redacted]
STUDY DESIGN	The study protocol referenced at the end 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 at the end of this report.

<table>
<tr><td></td><td>The main criteria included adults ≥18 years of age with adequate oral hygiene, in good general and oral health without any known allergy to commercial dental products or cosmetics, had a minimum of 20 natural teeth with scorable facial and lingual surfaces, had evidence of gingivitis and a minimum of 10 bleeding sites based on BI. Inclusion criteria also included absence of significant oral soft tissue pathology and advanced periodontitis based on the discretion of the dental examiner and absence of fixed or removable orthodontic appliance or removable partial dentures.</td></tr>
<tr><td>INVESTIGATIONAL STUDY MATERIALS</td><td>
<table>
<tr><th>Identification (ID)</th><th>Formula number</th><th>Product type</th><th>Batch Number</th></tr>
<tr><td>Alcohol containing Essential Oil (AEO) [redacted]</td><td>[redacted]</td><td>Investigational Product (IP)</td><td>[redacted]</td></tr>
<tr><td>[redacted] Hydroalcohol</td><td>[redacted]</td><td>Negative Control</td><td>[redacted]</td></tr>
<tr><td>[redacted] Dental Floss Waxed/Unflavored</td><td>[redacted]</td><td>Comparator</td><td>[redacted]</td></tr>
<tr><td>Colgate® Cavity Protection Toothpaste</td><td>[redacted]</td><td>Auxiliary Product</td><td>[redacted]</td></tr>
<tr><td>American Dental Association Referenced Toothbrush [redacted]</td><td>[redacted]</td><td>Auxiliary Product</td><td>NA</td></tr>
</table>
</td></tr>
<tr><td>DOSE AND MODE OF APPLICATION</td><td>Subjects were instructed to brush for at least one minute twice daily in their usual manner with the toothpaste (one full ribbon) and soft bristled toothbrush provided followed by rinsing twice daily for 30 seconds with 20 mL of the assigned mouth rinse or tap water depending on their randomization group. For those subjects randomized to the mouth rinse groups and to ensure the correct amount of mouth rinse was used twice daily, the study site provided each subject dosage cups marked at the 20 mL level and instructed subjects to fill their assigned mouth rinse to this point for each product use.</td></tr>
<tr><td>METHODOLOGY</td><td>Healthy subjects (approximately 40 subjects/4-treatment groups=160) who met the required inclusion/exclusion criteria were randomized in this 12-week, examiner-blind, single center, randomized, parallel-group controlled clinical study.

<u>Visit 1</u>

At Visit 1 (Baseline), subjects provided their consent, had their prior and concomitant medications/non-drug therapies, smoking, medical and dental histories recorded, and inclusion and exclusion criteria were reviewed.
A Baseline examination (oral hard and soft tissue assessment, gingivitis,</td></tr>
</table>

	bleeding of gingival margin, [redacted] and plaque) was performed for each subject. Baseline examinations included the following in this sequential order: oral hard and soft tissue assessment, MGI, BI, periodontal pocket depth, and bleeding for all gradable teeth at Visit 1 (and Visit 3 only), TP) and PMI. After the Baseline oral examination assessment, a complete dental prophylaxis was performed by qualified hygienist or dentist for thorough calculus and plaque removal and teeth were checked by another qualified hygienist or dentist to ensure completeness of prophylaxis. Qualifying subjects were randomly assigned to one of four study groups. Subjects received their assigned mouth rinse or marketed floss, a marketed fluoride-containing dentifrice, a marketed soft bristled toothbrush, dosage cups, and a timer at this visit to use throughout the study. Subjects were to begin use of their assigned test product following the label instructions. Subjects assigned to the flossing groups were to brush their teeth, then received instructions on flossing technique and had their teeth flossed by a trained professional or by themselves. Subjects assigned to the flossing groups attended flossing sessions at the site once daily during the week (five days). The second brushing of the day was to be completed and unsupervised at home. The remaining weekend days flossing and brushing was to be unsupervised at home. Subjects assigned to the rinse groups (marketed Listerine Cool Mint or negative control mouth rinse) were to brush their teeth and rinse once daily under supervision during the week (five days) and brush their teeth and rinse a second time each day during the week at home. During the weekends, subjects were to brush twice daily in their usual manner, followed by rinsing with their assigned marketed mouth rinse, unsupervised at home. Subjects were to maintain a diary card to document their daily brushing, flossing, or rinsing times if they could not get to the site or if this was used over the weekend. <u>Visit 2 (Day 28 ±2 days)</u> Subjects were to visit the clinical site for similar examinations [redacted] mentioned at Visit 1. Compliance was evaluated at Visit 2 by weighing residual volumes of returned mouth rinse, visually inspecting toothpaste tubes to ensure they used and the subject diary cards were also reviewed. Floss was evaluated for weekend use. Subjects were provided a new diary card and re-supply of investigational product to use through to Visit 3. <u>Visit 3 (Day 84 ± 3 days)</u> Subjects were to visit the clinical site for similar examinations mentioned at Visit 1 [redacted] Compliance was evaluated at Visit 3 by weighing residual volumes of returned mouth rinse, visually inspecting toothpaste tubes to ensure their use, and the subject diary cards were reviewed. Floss was also evaluated for weekend use. Female subjects of childbearing potential were to undergo a urine pregnancy test. No other oral hygiene procedures were permitted, including teeth cleaning, whitening or dental procedures except for an emergency treatment.

At each visit, Visit 1 (Baseline), Visit 2 (Day 28 ±2 days), Visit 3 (Day 84±3 days), subjects were asked not to practice oral hygiene for at least eight hours, but no more than 18 hours, and to refrain from eating for at least four hours prior to their clinical examinations.

Study Assessments:

Efficacy assessment included MGI, BI, TPI, and PMI and were assessed at Visit 1, Visit 2, and Visit 3. For each MGI, BI, TPI, and PMI scoring assessment, the findings were recorded into the electronic data capture (EDC) system. Oral assessments for gingival inflammation and bleeding and plaque were conducted at Baseline, 4-week, and 12-week visits by the Blinded Examiner.
Oral tissue tolerance was monitored through oral exam and the collection of adverse events.
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.

Statistical Analysis:

Sample size determination: A sample size of 37 completed subjects for each treatment group provides for 80% probability that the half-width for the confidence interval (CI) for the difference between two treatments will be no more than 0.2, assuming a standard deviation (SD) of 0.4. This sample size also provides 90% power to detect a standardized effect size of at least 0.8. Assuming a 7.5% dropout rate, 40 subjects were to be randomized to each treatment group to ensure 37 completers.

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.

Efficacy analyses: The primary efficacy endpoints were the interproximal mean TPI and interproximal mean MGI after 12 weeks of product use.

The secondary efficacy variables were interproximal mean TPI after four weeks of product use, interproximal mean MGI after four weeks, whole-mouth mean TPI and mean MGI at 4 and 12 weeks, interproximal and whole-mouth mean Bleeding Index 2, 3 (BI) at 4 and 12 weeks, interproximal and whole-mouth Percent Bleeding Sites at 4 and 12 weeks, and mean interproximal of the PMI at 4 and 12 weeks.

[redacted]

	Safety analyses: The number and percentage of subjects experiencing adverse events (AEs) and those experiencing IP-related AEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, preferred term, and IP. Investigational product-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 were presented. For the summary, the assessments were categorized as follows: Baseline, Week 4, Week 12, and Post-baseline (including Unscheduled, Week 4, and Week 12 visits).
MEASUREMENT AND/OR EVALUATION SCHEDULE	**Efficacy Evaluation**: The Blinded Examiner was to perform the examinations in the following order: MGI, BI, TPI, and PMI. MGI: Gingivitis was assessed 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 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 **Gingival Bleeding Index:** Bleeding index was assessed according to the Gingival BI. Each of the four gingival areas (disto-buccal, mid-buccal, mid-lingual, and mesio-lingual) around each tooth were 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 (TPI):** Plaque area was assessed using the TPI, on six surfaces (disto-buccal, mid-buccal, mesio-buccal and disto-lingual, mid-lingual, and mesio-lingual) of all scorable teeth, following disclosing: 0 = No plaque 1 = Separate flecks or discontinuous band of plaque at 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 surface 4 = Plaque covering 1/3, but less than 2/3 of surface 5 = Plaque covering 2/3 or more of a surface **Proximal Marginal Plaque Index (PMI):** Interproximal Plaque area was assessed using the PMI on the facial and lingual surfaces. Distal proximal and mesial proximal were assessed on

	all teeth including the distal of the second molar using the following scoring system: 0 =No plaque. 1 = Separate flecks of plaque covering less than 1/3 of the area. 2 = Discrete areas or bands of plaque covering less than 1/3 of the area. 3 = Plaque covering 1/3 of the area. 4 = Plaque covering more than 1/3 but less than 2/3 of the area. 5 = Plaque covering 2/3 or more of the area. [redacted] [redacted] **Safety Evaluations**: An oral examination was conducted at all visits to monitor oral hard and soft tissue 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 recorded into the EDC system. Changes from Baseline were recorded. Clinically significant findings were recorded as adverse events. All adverse events, for all subjects, whether serious or non-serious, observed and/or spontaneously reported, beginning from the time the informed consent is signed and dated, were captured in the EDC system. An expected event for some subjects may be a mild brief transient burning or tingling/cooling sensation of the oral soft tissues. This reported sensation will not be considered an adverse event. However, if these sensations are not mild, brief or transient they should be recorded as an adverse event.
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: 16 August 2018 Applicable Amendments: - Approval date: Not Applicable
SAFETY AND ADVERSE EVENTS	All AEs, 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. The severity of AEs were assessed by the medically qualified Investigator or designee using mild, moderate, and severe categorical descriptors.

MONITORING, QUALITY CONTROL, AND QUALITY ASSURANCE	The study monitoring was conducted as per the Sponsor´s requirements. The Study Site is subject to review by the IRB/IEC (if applicable), to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities.
CONCLUSION	• Reductions vs. the 5% hydroalcohol control (negative control) were statistically significant for AEO mouth rinse for both primary variables: interproximal mean TPI at 12 weeks (22.8% reduction) and interproximal mean MGI at 12 weeks (46.4% reduction). For the floss groups, reductions vs. negative control were statistically significant for interproximal mean MGI (26.4% and 21.6% reductions for flossing by hygienist and flossing under supervision), but reductions were not statistically significant for interproximal mean TPI (4.96% and 2.41% reductions). • Overall, the safety profile is consistent within all the treatment groups. Adverse events were similar in type and number across treatment groups. No serious AEs and no discontinuations related to the use of the investigational product were reported.