JOHNSON & JOHNSON CONSUMER INC.

SUMMARY CLINICAL STUDY REPORT

PROTOCOL TITLE:	Safety and Clinical Efficacy of Mouth Rinses in Type 1 and Type 2 Diabetics: Effect on Oral Soft Tissue, Plaque, and Gingivitis
PROTOCOL NUMBER:	CCSORC002281 Version 02 (Amendment 01) dated 02 DEC 2019
SITE STUDY NUMBER	1001
SPONSOR:	Johnson & Johnson Consumer Inc. [redacted]
STUDY SITE:	Salus Research, Inc. [redacted] Fort Wayne, IN 46825 US [redacted]
PRINCIPAL INVESTIGATOR:	[redacted]
KEY SITE STAFF	[redacted]

STUDY INITIATION DATE (First Subject First Visit):	02 December 2019
STUDY COMPLETION DATE (Last Subject Completed):	06 March 2020
SITE APPROVAL	**Name** [redacted] / **Signature and Date:**
SPONSOR REVIEW AND APPROVAL	**Name** [redacted] / **Signature and Date:**

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.

NOTE TO READER	This Clinical Study Report (CSR) is an update to previous CSR [redacted] final dated 22 July 2020). After this clinical trial, data analysis and CSR [redacted] were completed, post hoc review of the subjects' self-reported diabetes type and history revealed a pattern inconsistent with nationwide prevalence, i.e., there were more subjects who self-reported having Type 1 diabetes compared to those self-reporting Type 2 diabetes. A follow-up study (CCSORC004958) was conducted in April 2022, in which diabetes type and diabetes medications were verified in subjects who participated in the is study. The verification was done in interviews with the subjects by the study site physician where subjects showed the physician their diabetes medication, if any, and the physician confirmed the subject's diagnosis of Type 1 or Type 2 diabetes. The follow-up study showed that many subjects in clinical trial CCSORC002281 inaccurately reported their diabetes type. Details of verification study CCSORC004958 are documented in a CSR [redacted]. Once diabetes type was confirmed, the data from clinical trial CCSORC002281 that included analysis by diabetes type were re-analyzed. This updated CSR contains the results from clinical trial CCSORC002281 with the verified diabetes types for study subjects. It should also be noted that one subject (#10011044) who was in the original trial (CSORC002281) died before the updated diabetes type information was acquired in the follow-up study (CCSORC004958). For that subject, the originally reported diabetes type was used in the data analysis.
INTRODUCTION	It is estimated that 285 million people worldwide suffer from diabetes, a number which is projected to increase by about 50% by year 2030. Oral complications of diabetes include candidiasis, dental caries, tooth loss, gingivitis, lichen planus, neurosensory disorders (burning mouth syndrome), periodontitis, salivary dysfunction and xerostomia, and taste impairment. Periodontal disease is one of the main reasons for tooth loss among individuals with diabetes. Several controlled clinical trials have confirmed that subjects diagnosed with diabetes have a greater prevalence of periodontal diseases compared to healthy individuals.[1] Gingivitis, the mildest form of periodontal disease, is caused by the bacterial biofilm (dental plaque) that accumulates on teeth adjacent to the gingiva. This study was conducted to investigate the control of plaque related gingivitis in Type 1 and Type 2 diabetics with the additional use of essential oil containing mouth rinses.

OBJECTIVE(S)	The objective of this clinical trial was to evaluate mouth rinse formulations for oral soft tissue tolerance and efficacy in plaque/gingivitis prevention/reduction in subjects with Type 1 or Type 2 diabetes when used twice daily as an adjunct to tooth brushing during a 12-week treatment period.
STUDY DESIGN	The study protocol [redacted] 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 [redacted]. The main criteria included subjects ≥18 years of age with a good general and oral health without history of significant adverse effects, including sensitivities or suspected allergies, following use of oral hygiene products, adequate oral hygiene, a minimum of 20 gradable teeth including 4 molars with scorable both facial and lingual surfaces, self-reported diabetes Type 1 or Type 2-self reported; HbA1c level <7.0% for Type 1 diabetes and HbA1c level of <8.0% for Type 2 diabetes, mean gingival index ≥1.85 per the Modified Gingival Index (MGI) at Baseline, mean plaque index ≥1.95 per the 6-site Turesky modification of the Quigley-Hein Plaque Index (TPI) at Baseline, and ≥10% bleeding sites at Baseline. Other inclusion criteria included absence of fixed or removable orthodontic appliances or removable partial dentures, bruxism, or temporomandibular joint device, significant oral soft tissue pathology excluding plaque-induced gingivitis, and moderate/advanced periodontitis based on a clinical examination and discretion of the investigator/dental examiner.

INVESTIGATIONAL STUDY MATERIALS

Identification	Formula (F)/Universal Product Code (UPC)/Identification (ID) Number	Product Type
[redacted] Mouth Rinse [redacted]	[redacted]	Investigational Product (IP)
[redacted] Mouth Rinse	[redacted]	IP
[redacted] Mouth Rinse	[redacted]	IP- Negative Control
[redacted] Toothpaste	[redacted]	Auxiliary Product
[redacted] Toothbrush	[redacted]	Ancillary Product
[redacted] Floss	[redacted]	Ancillary Product

DOSE AND MODE OF APPLICATION

The subjects were instructed to rinse for 30 seconds with 20 mL of the assigned mouth rinse (morning and evening), after brushing for at least one minute using a full ribbon of a marketed toothpaste on the provided toothbrush.

METHODOLOGY

This was a single center, examiner-blind, randomized, parallel- group controlled clinical study with a study duration of 12 weeks (84 days± 4 days). Approximately, 165 (55 subjects per group) generally healthy subjects with Type 1 and 2 diabetes who met the required inclusion/exclusion criteria were planned to be enrolled/randomized in this clinical study to ensure that 150 subjects (50 subjects per group) completed the trial. The three groups included in the trial were:

1. [redacted] Mouth Rinse [redacted]
2. Marketed Alcohol Mouth Rinse [redacted]
3. [redacted] Mouth Rinse (negative control)

The study consisted of the following visits:

Visit 1 (Screening)

At Visit 1, subjects were consented at the clinical site. Their prior and concomitant medications/non-drug therapies, demography, smoking,

	medical and dental histories were recorded and inclusion and exclusion criteria were reviewed. In addition, a blood sugar test (HbA1c) was performed to confirm level of control (fasting was not required). Subjects with Type 1 diabetes with HbA1c level <7.0% and subjects with Type 2 diabetes with HbA1c level <8.0% continued participation in the study. **Visit 2: Baseline (Day 0), Visit 3 (Day 7 ± 2 days), Visit 4 (Day 42 ± 3 days), and Visit 5 (Day 84 ± 4 days)** At Visits 2, 3, 4, and 5, subjects presented to the clinical site for examinations after refraining from oral hygiene for at least 8 hours, but no more than 18 hours, and refrained from eating for at least 2 hours prior to that examination. Inclusion/exclusion criteria, adverse event (AE) assessment, and concomitant medications/non-drug therapies were reviewed to ensure subjects were eligible to continue participation in the study. Female subjects of childbearing potential were given a urine pregnancy test at Visits 2 and 5. Each subject underwent an oral examination (oral hard and soft tissue assessment) and assessment of the periodontal pocket depth of all teeth for inclusion. Baseline examinations included MGI, TPI, and Expanded Bleeding Index (EBI). TPI was assessed at Visits 2-5. MGI and EBI were assessed at Visits 2, 4, and 5. After the baseline oral examinations, a complete dental prophylaxis was performed by a qualified professional. Teeth were checked to ensure completeness of prophylaxis by another qualified professional prior to the subject being dismissed. Qualifying subjects were randomly assigned to one of the three groups at Visit 2 and received their assigned mouth rinse, a marketed fluoride-containing dentifrice, floss (if flossing was part of their normal oral care routine), a marketed soft bristled toothbrush, and a timer (if needed) at this visit to use throughout the study. Subjects used their assigned study products following the label instructions. The first product use (brushing and rinsing) was conducted at the site under supervision of study personnel. Subjects were asked if they experienced any AEs after the first product use. All other brushing and rinsing was unsupervised. Subjects were instructed to brush twice daily in their usual manner, followed by rinsing with their assigned mouth rinse formulation for a timed 30 seconds. Subjects were given oral/written instructions and a diary card to document their twice daily brushing and rinsing times. At Visit 5, subjects were also given a Perception Questionnaire and received a complete dental prophylaxis by a qualified professional. Compliance was evaluated at Visits 3, 4, and 5 by weighing residual volumes of returned mouth rinse, visually inspecting toothpaste for use, and reviewing the subject diary cards. Throughout the study, 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.

End of Study:
For subjects whose participation was discontinued during this trial, end of study evaluations were to be completed as soon as possible after discontinuation.

Study Assessments:
Oral tissue tolerance was assessed at Visits 2-5. TPI was assessed from Visits 2 to 5. MGI and EBI were assessed at Visits 2, 4, and 5.

Oral tissue tolerance was monitored through oral examination and 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 to be photographed and sent to the Sponsor.

Statistical Analysis:
Sample Size Determination: A sample size of 50 completed subjects per IP group provides approximately 80% confidence that for a product group, the difference is no more than 0.065 between the observed and population proportions of subjects with AE, provided that the population proportion of subjects with AE is no higher than 0.15 (i.e., the half-width of an 80% confidence interval would be no higher than 0.065). This sample size also provides approximately 80% confidence that the difference is less than 0.06 between the observed and population proportions provided that the population proportion of subjects with AE is no higher than 0.12. To allow for a dropout rate of approximately 10%, 55 subjects were planned to be randomized in each group.

This sample size also provides at least 90% power to detect pairwise differences in population IP means of 0.44 for whole-mouth mean MGI and 0.3 for whole-mouth mean TPI based on two-sided tests at the 0.05 level of significance, assuming population standard deviations (SD) of 0.44 for mean MGI and 0.45 for mean TPI. The estimated population SD and IP mean differences were conservative estimates based on two previous 3-month plaque/gingivitis clinical trials using the same examiner as this trial.

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 to be used in the place of the Chi-Square test.

Efficacy Analyses: The primary endpoints were whole mouth mean MGI and whole mouth mean TPI after 12 weeks of product use.

Secondary endpoints were whole mouth mean TPI after 1 and 6 weeks, whole mouth mean MGI after 6 weeks, whole mouth mean EBI after 6 and 12 weeks, and percent of bleeding sites, based on the EBI after 6 and 12 weeks.

Between-IP comparisons were based on a repeated measures mixed model, including terms for IP, diabetes type, and visit, and the corresponding baseline value as a covariate. IP-by-visit and Baseline-by-visit terms were included in order to do comparisons at specific visits.

Model based p-values, estimated differences in means, and 95% confidence intervals were presented. The following between-IP comparisons were performed:

- [redacted] vs. [redacted] (negative control)
- [redacted] mouth rinse vs. [redacted] (negative control)

Each statistical test was carried out at the 0.05 level of significance, two-sided. Considering that the purpose of this trial was to separately evaluate [redacted] and [redacted] mouth rinse in this subject population, no multiple comparison adjustment was made.

Perception data analysis: The perception questionnaire was used to collect each subject's perception data at 12 weeks. The number and percentage of subjects by response for each question was presented by IP.

For the ordinal response questions, means and SDs were displayed. Between-IP comparisons were performed based on an ANOVA model with IP as a factor. Model-based p-values, differences between IP means, and 95% confidence intervals were presented. Each statistical test was carried out at the 0.05 level of significance, two-sided. In addition, statistical testing at the 0.10 level of significance was presented.

Subgroup Analysis: For subjects with Type 2 diabetes, subgroup analyses were performed for each primary and secondary efficacy endpoint, separately for subjects with HbA1c <7.0% and subjects with HbA1c ≥7.0%. For each subgroup and endpoint, between treatment comparisons were based on a repeated measures mixed model, including terms for IP and visit, and the corresponding baseline value as a covariate. IP-by-visit and Baseline-by-visit terms were included in order to do comparisons at specific visits.

Additional Analysis: Summary statistics were provided by IP group at Baseline and post-baseline visits. In addition to summary statistics for primary and secondary variables, frequency tables were provided based on:

- Site-wise scores at Baseline vs. post-baseline
- Improvement status from Baseline (improved, not changed, or worsened)
- Healthy (MGI=0 or 1) and Non-healthy (MGI=2, 3, or 4) sites
- Plaque-Free (PI=0 or 1) and Plaque (PI=2, 3, 4, or 5) sites
- Non-Bleeding (EBI=0) and Bleeding (EBI=1 or 2) sites

Post-hoc analysis: Summary statistics were provided by IP group at Baseline and post-baseline visits.

- For subjects with Type 1 diabetes, subgroup analysis was performed for each primary and secondary efficacy endpoint

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Percent of Healthy Sites (BI=0 and MGI=0 or 1) and its sensitivity analysis

Criteria for classifying MGI and EBI as a healthy (=1) or not healthy (=0) indicator variable are listed below:
<table>
<tr><th>MGI</th><th>EBI</th><th>Value of MGI/EBI for Primary Analysis</th><th>Value of MGI/EBI for Sensitivity Analysis 1</th><th>Value of MGI/EBI for Sensitivity Analysis 2</th></tr>
<tr><td>0 or 1</td><td>0</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>0 or 1</td><td>1 or 2</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>0 or 1</td><td>Missing</td><td>Missing</td><td>0</td><td>1</td></tr>
<tr><td>2, 3, or 4</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>2, 3, or 4</td><td>1 or 2</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>2, 3, or 4</td><td>Missing</td><td>0</td><td>0</td><td>0</td></tr>
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<u>Safety Analysis</u>: The number and percentage of subjects with treatment-emergent AEs (TEAEs) and those experiencing IP-related AEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, preferred term, and IP. IP-related AEs included events marked as being possibly, probably, or very likely related to study product. Subjects who experienced Serious AEs (SAEa)and AEs resulting in withdrawal from IP were listed.
A summary tabulation of conditions and irritation scores by anatomical site based on the oral examinations in the study was presented by timepoint and by IP.
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<td>MEASUREMENT AND/OR EVALUATION SCHEDULE</td>
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Efficacy Evaluation:
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: oral hard and soft tissue examination, MGI (if applicable), EBI (if applicable), pocket depth (Visit 2 only), and TPI. Each subject was examined by this same examiner throughout the course of the trial.

Modified Gingival Index (MGI)
Gingivitis was assessed using 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,
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	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 according to the EBI on 168 sites. A periodontal probe with a 0.5 mm diameter tip was inserted into the gingival crevice and swept around the tooth at an angle of approximately 60 degree, while in contact with the sulcular epithelium. Each of 6 gingival areas (distobuccal, mid-buccal, mesiobuccal, distolingual, mid-lingual, and mesiolingual) 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 scored at all visits using the TPI, on 6 surfaces (distobuccal, mid-buccal 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 Safety assessment: An oral examination was conducted at all examination visits to monitor oral soft and hard tissues tolerance to the trial products. Buccal and sublingual mucosae, lips/labial mucosa, mucobuccal fold, gingiva, tongue, hard and soft palate, uvula, oropharynx, teeth and dental restorations were to be examined and findings were recorded in the electronic data capture (EDC) system. Changes from Baseline were recorded. Clinically significant findings were recorded as AEs in the EDC system. The Investigator assessed the relationship to the treatment. At the discretion of the medically qualified clinical examiner, common findings or "aberrations" were typically recorded as oral abnormalities and not as AEs.
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: 25 November 2019 Applicable Amendments: Amendment#1 - Approval date: 16 December 2019

SAFETY AND ADVERSE EVENTS	All AEs and 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 trial 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.
CONCLUSIONS	The mouth rinses in this clinical trial [redacted] met the trial efficacy objective by reducing plaque and gingivitis significantly more than the [redacted] negative control in subjects with Type 1 and Type 2 diabetes when used twice daily as an adjunct to tooth brushing during a 12-week treatment period. The mouth rinses also presented acceptable oral soft tissue tolerance after 12 weeks of product use, with no new safety concerns observed. In addition, the mouth rinses met the secondary objectives of reducing plaque after 1 and 6 weeks, reducing gingivitis after 6 weeks, and reducing gingival bleeding and percent bleeding sites after 6 and 12 weeks. • Whole mouth mean TPI was significantly reduced by 13.2% and 24.7% [redacted] compared to [redacted] after 12 weeks of product use ($p<0.001$ for all comparisons). Similar results were seen in the whole mouth mean TPI after 1 and 6 weeks of product use. • Whole mouth mean MGI was significantly reduced by 32.8% and 37.2% for [redacted] compared to [redacted] after 12 weeks of product use ($p<0.001$ for all comparisons). Similar results were seen in the whole mouth mean MGI after 6 weeks of product use. • Whole mouth mean EBI was significantly reduced by 72.6% and 68.7% [redacted] compared to [redacted] after 12 weeks of product use ($p<0.001$ for all comparisons). Similar results were seen in the whole mouth mean percent bleeding sites after 6 weeks of product use. • Whole mouth mean percent bleeding sites, based on the EBI, was significantly reduced by 72.6% and 71.0% [redacted] compared to [redacted] after 12 weeks of product use ($p<0.001$ for all comparisons). Similar results were seen in the whole mouth mean EBI after 6 weeks of product use.

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