A CLINICAL STUDY TO ASSESS EFFICACY OF ClōSYS FLAVORED ORAL RINSE IN HUMAN SUBJECTS IN CONTROLLING ORAL MALODOR

FINAL CLINICAL SITE REPORT
(Report for Oral Rinses X and Y)

Protocol: UHRG-RPR-Oral Rinse Malodor-ADA-2016

University Health Resources Group
5714 Canterbury Drive
Culver City, California 90230

March 2017

Title of Project:	Efficacy of ClōSYS oral rinse product in human subjects in controlling oral malodor (Oral Rinses X and Y)
Protocol:	UHRG-RPR-Oral Rinse Malodor-ADA-2016
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3/10/17
Date

CLINICAL SITE REPORTING SUMMARY

Study Objective

The objective of this study was to assess the efficacy of ClōSYS Flavored Oral Rinse product in human subjects in controlling oral malodor, in partial fulfillment of the requirements for recognition by the American Dental Association (ADA).

Brief Description of the Study Procedures

Study Population: Enrolled a total of fifty (50) healthy male and female subjects between the ages of 21-65 years with an average organoleptic intensity rating of at least 2.6 but no higher than 4.5 on an intensity scale of 0-5 following 12-18 hours oral hygiene abstention.

Number and Location of Centers: Single; 7721 S. Painter Ave., Whittier, CA 90602

Study Design: *In-vivo*; a single-center; randomized; double-blind; 2-way cross-over; 2 independent groups; each subject of either active or control group will be crossed over to the other group after the washout period; 8 weeks comprising:

- Screening and enrollment
- Phase I treatment period (3 week)
- Washout period (2 week)
- Phase II treatment period (3 week)

Number of Exposures (Uses): Twice a day after tooth brushing, each in the morning and in the evening, with 15ml of assigned oral rinse for each subject; Off-site.

Duration of Each Exposure (Use): 30 seconds

Blinding: Double blind

Overall Duration of Study: 3 week (phase I treatment period) + 2 week (washout period) + 3 week (phase II treatment period)

Method of Patient Assignment: Randomized

Study Type: Breath Freshener Oral Rinse

Primary Efficacy Variable(s): Average (across judges) organoleptic intensity rating rated at baseline, 1 week post initiation of product use, 2 weeks post initiation of product use, and 3 weeks post initiation of product use. Average (across judges) organoleptic intensity rating rated at baseline two, 1 week post reinitiating of product use, 2 weeks post reinitiating of product use, and 3 weeks post reinitiating of product use.

Study Arms: ClōSYS justRIGHT MILD MINT Oral Rinse (ClōSYS Flavored Oral Rinse), Placebo ClōSYS Oral Rinse Solution (Placebo Oral Rinse).

Start Date: August 2016

End Date: 01/29/2017

Status: Completed

CLINICAL SITE REPORT

Introduction

A randomized, 2-way cross-over trial was designed and conducted to evaluate the effect of ClōSYS Oral Rinse product on oral malodor.

Study Objective

The purpose of this study was to assess the efficacy of ClōSYS Flavored Oral Rinse product (ClōSYS justRIGHT MILD MINT Oral Rinse) in human subjects in controlling oral malodor, in partial fulfillment of the requirements for recognition by the American Dental Association (ADA).

Protocol Approvals: Prior to the conduct of the study, protocols and pertinent documents were submitted to and approved by Biomed IRB, Biomedical Research Institute of America, P.O. Box 600870, San Diego, CA 92160. An informed letter of consent was reviewed and signed by each of the study participants before the initiation of the project. A copy of the signed informed letter of consent was provided to the subject. The protocol was approved by ADA.

Overall Study Design — Description

This was an *in-vivo*, eight-week, single-center, randomized, double-blind (subject/investigator), 2-way cross-over design clinical trial. Fifty adult volunteers, aged 21 to 65 years, with a slight to strong intrinsic oral malodor of at least 2.6 but no higher than 4.5 on an intensity scale of 0-5, as determined by a panel of trained odor judges, following 12-18 hours oral hygiene abstention, were enrolled. There were two groups. Each subject of each group was crossed over to the other group after the washout period. In the first phase, 25 subjects were randomly assigned to the active group; the other 25 subjects were assigned to the control group. In the second phase, the participants were crossed over to the other group. (Table 1).

<u>Screening</u>

Every potential subject was interviewed by the assigned staff member and was provided an Informed Consent Form (ICF). Subjects who met eligibility criteria and signed the ICF then had

an Oral Screening Examination performed by a study dentist. Potential subjects who satisfied all oral examination criteria maintained eligibility.

After review of the results of the ICF, Screening Interview, and Screening Oral Examination, the Principal Investigator determined whether or not a subject was enrolled in the study. The following procedures were conducted:

- Informed Consent: The purpose and procedures of the Study were described to the subject. The subject had the opportunity to ask questions about the study in private and upon permission signed the ICF. The HIPAA form was also explained to the subject at this stage in Screening.
- Screening Interview: The subject was asked inclusion and exclusion questions, demographics, smoking or non-smoking, and date of last professional dental cleaning. A brief medical history of each subject was recorded.
- Medical History and Medications: A brief medical history of each subject was recorded.
- Dental Health History: The subject was asked to report the date of last scaling and root planing or polishing and date of last professional cleaning.
- Oral Examination: The oral cavity was evaluated for any mucosal irritation, lesions or pathology. Each evaluation included face lymph nodes, lips, buccal mucosa, hard and soft palates, oropharynx, tongue, floor of the mouth, edentulous ridges and teeth.
- To be eligible for participation in the Study, subjects had no clinical evidence of mucosal inflammation and/or lesions or other visual evidence of oral disease.

Breath Examination Instruction

Subjects were given following instructions for the baseline and subsequent weekly examination visits. Subjects abstained from all oral hygiene regimens including brushing, using mouth rinse, and cleaning their tongue for 12 hours. Subjects abstained from eating 8 hours prior to their scheduled visit and abstained from drinking at least 2 hours prior to their visit. Subjects also abstained for 12 hours from last intake of alcohol, foods containing sulfur compounds such as garlic or onion, scented cosmetics, and smoking or using any tobacco products. They had 24 hours abstention from medicated lozenges, mints, sweets or gum that contain antimicrobial agents, including but not limited to, xylitol, essential oils, cetylpyridinium chloride, chlorine dioxide, and zinc. They refrained from elective dental procedures. Subjects did not use any other oral rinse or mouthwash. Prior to breath examinations, subjects were instructed to have their mouth closed for at least 2 minutes.

Study Formulations

ClōSYS justRIGHT MILD MINT Oral Rinse (ClōSYS Flavored Oral Rinse), Placebo ClōSYS Oral Rinse Solution (Placebo Oral Rinse). ClōSYS Flavored Oral Rinse product containing 0.1% stabilized chlorine dioxide (sodium chlorite) in an aqueous solution was supplied by Rowpar Pharmaceuticals in 16oz. white, opaque bottles, along with measuring cups. The Study Placebo was a close match in taste and appearance to the Study Formulation but without stabilized chlorine dioxide. The formulations were labeled as Oral Rinse X and Oral Rinse Y.

Inclusion Criteria

Subjects who met the following criteria were enrolled in the study:

- Had read, signed, and received a copy of the Informed Consent prior to Study initiation,
- Was able to follow verbal and/or written instructions, perform oral hygiene procedures and return to the test facility for specified Study examinations,
- Was between the ages of 21 and 65 years of age, male or female,
- Had normal oral interior cheek wall tissues,
- Was in good general health as determined by medical history and clinical judgment that no severe or debilitating disease existed that impeded participation in the Study,
- Had an average organoleptic intensity rating of at least 2.6 but maximum 4.5 on an intensity scale of 0-5.

Exclusion Criteria

Subjects were excluded from study participation where there was evidence of:

- Pregnancy or nursing per subject report,
- Diagnosis of Xerostomia, including medication induced Xeriostomia,
- Any oral or extraoral piercing that interferes with the ability to perform study procedures and/or clinical assessments in the mouth,
- Fixed or removable oral appliances, such as orthodontic brackets or retainer, partial or complete dentures,
- Advanced periodontal disease or excessive gingival recession, per Investigator/Examiner discretion,
- A known allergy or sensitivity to products used in the study,
- Unwillingness to abstain from all other oral hygiene products other than those prescribed for the duration of the study,
- Heavy deposits of calculus, either supergingival and/or subgingival, per Investigator/Examiner discretion
- A history of severe transmittable infectious disease (hepatitis, HIV, tuberculosis),
- A medical or dental condition that was unduly affected by participation in the study, per Investigator discretion,
- Any other condition that Principal Investigator considered interfering with the study,
- Smokers.

Enrollment

Each subject who completed the screening period of the study was registered or randomized and assigned a unique sequential subject identification number. This number was used to identify the subject and was used on all applicable study documentation related to that subject. The subject identification number remained constant throughout the first phase. A new subject identification number that is 100 higher than the original number was used throughout the second phase for a

statistical purpose (e.g. 201 is used as a new subject identification number of subject 101 for the second phase).

The written Informed Consent document was signed and personally dated by the subject and completed to a fully executed Informed Consent document and processed per the Institution's Standard Operating Procedures.

Before subjects were entered into the study, a copy of the written Institutional Review Board approval of the protocol, Informed Consent Form, and all other applicable subject information and/or recruitment material were on file at the Institution.

Materials

Each subject received one bottle (16oz) of either ClōSYS Flavored Oral Rinse, or Placebo. The bottles of the respective Oral Rinse were replaced every week. Additionally, 120 measuring cups, one tube of Crest Cavity Protection Toothpaste, Regular (8.2oz) and one ClōSYS toothbrush was provided to each subject. Upon depletion of the toothpaste, an additional tube was provided. Each subject received one toothbrush once every two weeks.

Calibration of Judges

The organoleptic evaluation panel consisted of three organoleptic judges (OJs) who were trained and calibrated prior to the initiation of the study. These judges have participated in oral malodor studies for many years. We have developed a program for training organoleptic judges over the last twenty plus years that we have been involved in oral malodor clinical trials.

It is important that the individuals who serve as odor judges have a good sense of smell. This was verified by using a simple smell identification test (Sensonics Inc., Haddon Heights, NJ, USA).

The OJs completed a 4-phase training protocol based on the American Society of Testing and Materials standards (ASTM): (i) introduction to sensory scales, n-butanol reference, sniffing techniques; (ii) pretraining measurements; 20 samples of varying intensities of four unpleasant and three pleasant odorants; (iii) exercises assessing quality, intensity, ranking, and matching; and (iv) post-training measurements.

After the basic training the OJs sniffed 15 subjects to confirm that they were all calibrated.

Study Visits

Different activities for data collection at each visit are summarized in Table 2.

Baseline Visit

The initial baseline visit took place on the same day of the initial screening visit. Screening documentation was revisited and it was verified that all the data had been recorded. The oral examination was performed. A panel of three trained calibrated judges assessed the breath. In order to create reproducible assessment, subjects were instructed to close their mouths and

breathe through their nose for two minutes. After two minutes, the subject was instructed to count out loud (1-20) while the subject was exhaling through the mouth. During this time, the odor judges assessed the odor intensity at approximately 10 centimeters from the subject's mouth. The judges gave an organoleptic score based on a 6-level scale described in Table 3. The subject was directed to the staff member for dispensing of the proper product according to randomization and patient log. The subject was instructed to continue with normal oral-hygiene practice during the entire study, including tooth brushing but omitting any use of oral rinses or mouthwashes other than the study products. The subject was given a calendar diary to record uses of the assigned products. Subjects were instructed to return all used and unused products each week during their visit. Subsequent study visits were scheduled at one (1), two (2), and three (3) weeks after the baseline visit. After a 2-week washout period, the subject was scheduled again one (1), two (2), and three (3) weeks after the second baseline visit.

Visit 1 – One Week Post Initiation of Product Use

This study visit took place one (1) week post initiation of subject's use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 2 confirmed.

Visit 2 – Two Weeks Post Initiation of Product Use

This study visit took place two (2) weeks post initiation of subject's use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 3 was confirmed.

Visit 3 – Three Weeks Post Initiation of Product Use

This study visit took place three (3) weeks post initiation of subject's use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The appointment date scheduled for Visit 4 was confirmed. Oral hygiene products for the washout period were dispensed.

Washout Period

Subjects had a two week "washout" period where they did not use any study materials but continued with normal oral-hygiene practices, including tooth brushing using Crest Cavity Protection Toothpaste, Regular but omitting any use of oral rinses or mouthwashes.

Baseline Two – Five Weeks Post Initiation of Product

This second baseline visit took place five (5) weeks post initiation of subject's initial use of product. Screening documentation was revisited and any new medical history on respective documents was updated. It was verified that all the data had been recorded. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for baseline one visit. The subject was directed to the staff member for dispensing of the proper product according to randomization and patient log. The subject was instructed to continue with normal oral-hygiene practice during the entire study, including tooth brushing but omitting any use of oral rinses or mouthwashes other than the study products. The subject was given a calendar diary to record uses of the assigned product. The subject was instructed to return all used and unused products. The appointment date scheduled for Visit 5 was confirmed.

Visit 5 – One Week Post Reinitiation of Product Use

This study visit took place one (1) week post reinitiation of subject's restart of use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 6 was confirmed.

Visit 6 – Two Weeks Post Reinitiation of Product Use

This study visit took place two (2) weeks post reinitiation of subject's restart of use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 7 was confirmed.

Visit 7 – Three Weeks Post Reinitiation of Product Use

This study visit took place three (3) weeks post reinitiation of subject's restart of use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product.

The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded.

Results and Discussion

None of the enrolled subjects in groups X and Y dropped during Phase I of the study. However, 3 subjects in group X and 2 subjects in group Y dropped in Phase II. Major reasons for withdrawal were commuting and scheduling issues.

There were no adverse events reported by subjects within the duration of the study.
Oral soft tissue examinations found no evidence of anomalies of soft and hard palate, buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands, and the tonsilar and pharyngeal areas in any of the subjects before and after the use of test products during each phase.

The distribution of gender, age, and race of subjects enrolled in the study is summarized in Tables 4, 5, and 6. The assignment of a subject to a group was based on randomization table and sequential to enrollment. Nonetheless, representation from both genders, over the target span of age, and different races was present in the study.

Organoleptic scores of each group and at each visit were recorded for both Phases I and II. The raw data was processed for statistical distribution. The values for mean, standard deviation (SD), and standard error of the mean (SEM) are presented in Tables 7 and 8. The results are also summarized in Figure 1. The mean values for organoleptic score for the two groups at the respective baselines were not significantly different; mean organoleptic score for groups X and Y at the baseline of Phase I were 3.60 and 3.63 and at Phase II were 3.25 and 3.05, respectively. The mean organoleptic score for group X decreased at a much more rapid rate during each visit compared to group Y. Mean organoleptic score in Phase I dropped from 3.60 at baseline to 1.15 at visit 3 in group X and from 3.63 at baseline to 2.65 at visit 3 in group Y. Similarly, mean organoleptic score in Phase II dropped from 3.25 at baseline to 1.25 at visit 3 in group X and from 3.05 at baseline to 2.83 at visit 3 in group Y. Importantly, the observation of Phase I was reproducible in Phase II after the crossover. The SEM values for all data points in Phase I and Phase II were between 0.07 and 0.13 exhibiting minimal variation in the distribution of the data.

The analysis was also performed by pooling the organoleptic scores from Phase I and II for each group. The results are summarized in Table 9 and Figure 2. Mean organoleptic score dropped from 3.43 at baseline to 1.20 at visit 3 in group X and from 3.34 at baseline to 2.74 at visit 3 in group Y. The pooled SEM values for all data points were between 0.079 and 0.080 exhibiting minimal variation in the distribution of the data.

Net reduction in oral malodor is the difference in organoleptic score at baseline and visit 3. Change in organoleptic score at visit 3 compared to organoleptic score at respective baseline was calculated for each group and for Phase I and II. The results are presented in Table 10 and Figure 11. Oral Rinse X decreased the mean organoleptic score by 2.449 and 1.999 in Phase I and II

respectively. Whereas, Oral Rinse Y decreased the mean organoleptic score only by 0.973 and 0.211 in Phase I and II, respectively.

Mean difference, Standard Error (SE) difference, and *p*-values at each visit for Oral Rinses X vs. Y for Phase I and II are summarized in Tables 11 and 12. It is evident that Oral Rinse X exhibited statistically significant reduction of oral malodor compared to Oral Rinse Y.

Label Key

Rowpar Pharmaceuticals, Inc. released the label key after completion of the study and data analysis. The products were labeled as follows:

- ClōSYS Flavored Oral Rinse was labeled as Oral Rinse X
- ClōSYS Placebo Oral Rinse was labeled as Oral Rinse Y

Conclusions

The data presented in Tables 7 to 12 and Figures 1 to 3 and label key support the following conclusions:

1. ClōSYS Flavored and Placebo Oral Rinses tested in this study do not exhibit any adverse effects and therefore are safe to oral tissues.
2. The use of ClōSYS Flavored Oral Rinse twice daily for up to three weeks provides statistically significant reduction in oral malodor compared to the reduction in oral malodor by placebo.
3. The use of ClōSYS Placebo Oral Rinse twice daily for up to three weeks provides statistically less reduction in oral malodor compared to the reduction in oral malodor by ClōSYS Flavored Oral Rinse.

Table 1. Study Design

Group	Product	Number of Subjects	Description
X, Y	ClōSYS Flavored Oral Rinse(CFOR) & Placebo Oral Rinse	50 subjects randomly assigned to two groups	25 subjects will start with the CFOR observe washout period, and switch to Placebo.
			25 subjects will start with the Placebo, observe washout period, and switch to CFOR.

Table 2. Data Collection Schedule and Visits

Procedures	Phase I Visit				Washout	Phase II Cross-over Visit			
	Base-line 1	1	2	3	2-week	Base-line 2	6	7	8
Screening Documentation	X					X			
Oral Examination	X	X	X	X		X	X	X	X
Health Changes		X	X	X			X	X	X
Malodor Level	X	X	X	X		X	X	X	X
Data Recorded	X	X	X	X		X	X	X	X
Product & Log Dispensed	X	X	X			X	X	X	
Unused Product & Log Collected		X	X	X		X	X	X	X
Follow-Up Visit Scheduled	X	X	X	X		X	X	X	
Oral Hygiene Instructions Given	X					X			

Table 3. American Dental Association Organoleptic Intensity Rating

ADA Organoleptic Intensity	
Rating	**Odor Intensity**
0	Malodor cannot be detected
1	Questionable malodor, barely detectable
2	Slight malodor, exceeds the threshold of malodor recognition
3	Malodor is definitely detected
4	Strong malodor
5	Very strong malodor

Table 4. Gender Distribution within Study Groups

Group	Female		Male		Total Number
	Number	%	Number	%	
X	20	76.9	6	23.1	26
Y	14	56.0	11	44.0	25

Table 5. Age Distribution in Years within Study Groups

Group	Minimum	Maximum	Median	Mean	SD	SEM
X	21	60	40	40.61	12.91	2.53
Y	21	61	40	39.44	15.29	3.06

Table 6. Ethnicity Distribution within Study Groups

Ethnicity	X		Y	
	Number	%	Number	%
Asian Oriental	1	3.85	0	0.00
Black (African American)	1	3.85	0	0.00
Caucasian	3	11.54	7	28.00
Hispanic	20	76.92	16	64.00
Asian Indian	0	0.00	1	4.00
Multi-Racial	1	3.85	1	4.00
Total	26	100	25	100

Table 7. Malodor Mean Values for Phase I

Group (n)	Baseline -1			Visit-1			Visit-2			Visit-3		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
X (26)	3.60	0.63	0.12	2.19	0.51	0.10	1.45	0.51	0.10	1.15	0.37	0.07
Y (25)	3.63	0.62	0.12	3.03	0.64	0.13	2.73	0.60	0.12	2.65	0.56	0.11

Table 8. Malodor Mean Values for Phase II

Group (n)	Baseline -2			Visit-1			Visit-2			Visit-3		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
X (23)	3.25	0.52	0.11	2.08	0.56	0.12	1.48	0.60	0.13	1.25	0.47	0.10
Y (23)	3.05	0.38	0.08	2.89	0.47	0.10	2.83	0.50	0.10	2.83	0.50	0.10

Table 9. Malodor Mean Values for Phase I and Phase II Combined

Group	Baseline		Visit-1		Visit-2		Visit-3	
	Mean	Pooled SEM	Mean	Pooled SEM	Mean	Pooled SEM	Mean	Pooled SEM
X	3.43	0.079	2.14	0.079	1.47	0.079	1.20	0.079
Y	3.34	0.080	2.96	0.080	2.78	0.080	2.74	0.08

Table 10: Organoleptic Change Scores Compared to Baseline in Phase-I and Phase-II

Group	Phase-I					Phase-II				
	n	Mean	SD	SEM	p-value*	n	Mean	SD	SEM	p-value*
X	26	-2.449	0.705	0.138	**0.328×10^{-29}**	23	-1.999	0.541	0.113	**0.442×10^{-22}**
Y	25	-0.973	0.704	0.141	**0.699×10^{-9}**	23	-0.211	0.45	0.095	**0.1517**

*p-values for change of the mean from respective baseline

Table 11: Mean differences, Standard Error difference, and *p*-value at each visit during Phase I

Visit	Oral Rinse X vs. Y		
	Mean difference	SE difference	p-value
Baseline	-0.024	0.156	0.8772
1	-0.835	0.156	0.2892×10^{-6}
2	-1.281	0.156	0.6456×10^{-13}
3	-1.500	0.156	0.1420×10^{-16}

Table 12: Mean differences, Standard Error difference, and *p*-value at each visit during Phase II

Visit	Oral Rinse X vs. Y		
	Mean difference	SE difference	p-value
Baseline	0.198	0.162	0.2235
1	-0.813	0.162	0.1455×10^{-5}
2	-1.352	0.162	0.3512×10^{-13}
3	-1.584	0.162	0.6328×10^{-17}

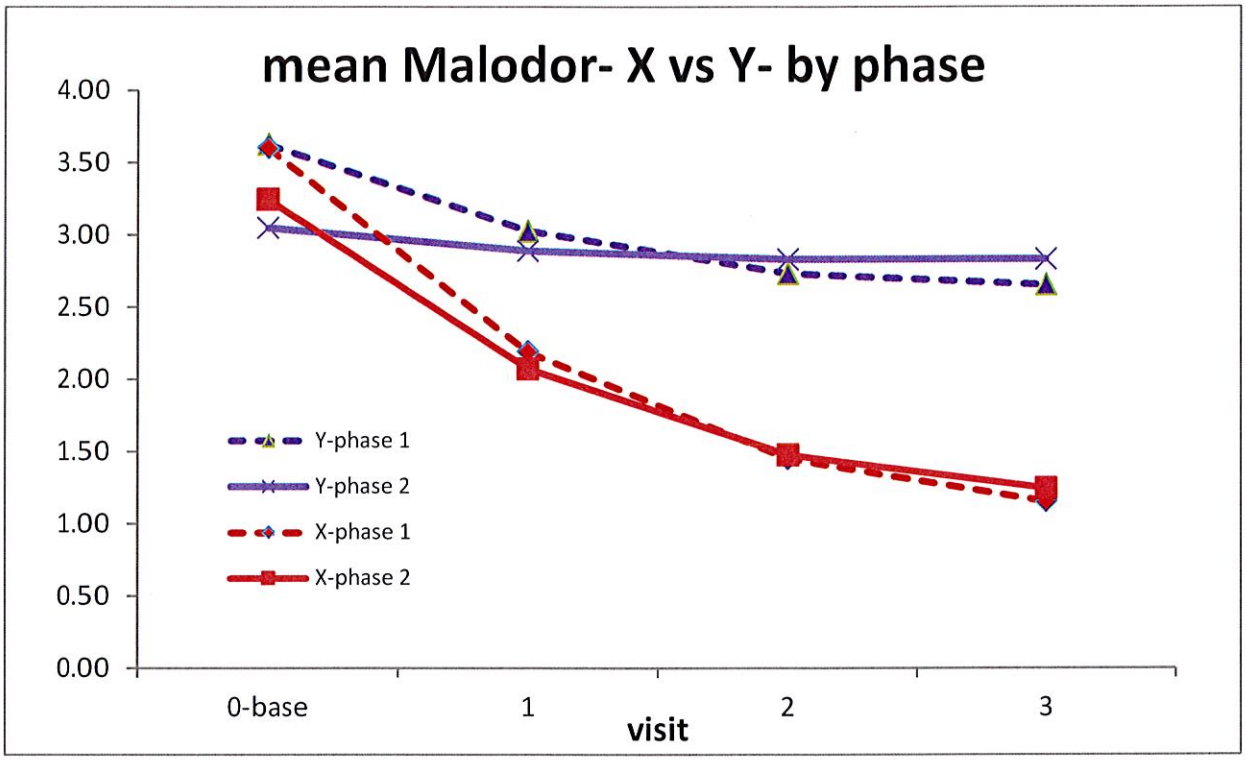

Figure 1. Trend in Mean Malodor for Groups X and Y for Individual Phases (data from Table 7 and Table 8).

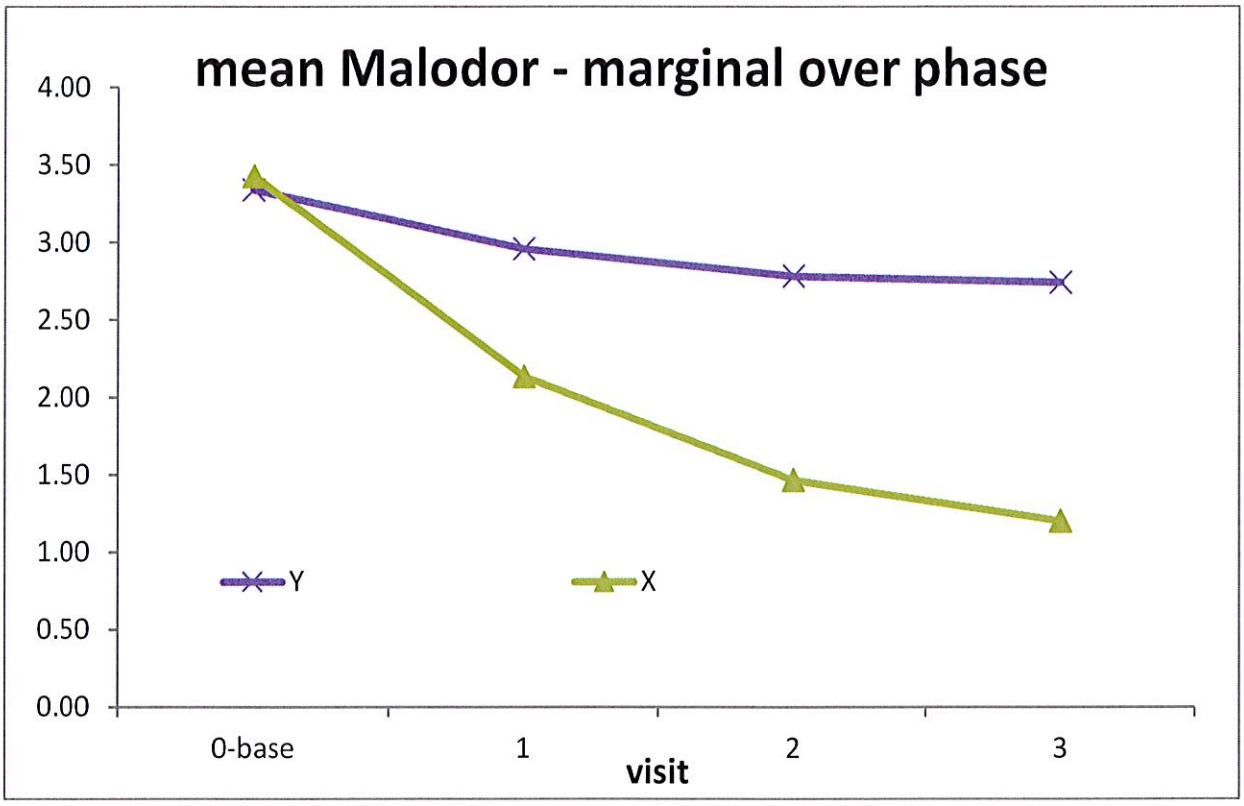

Figure 2. Trend in Combined Mean Malodor for the Two Phases for Groups X and Y (data from Table 9).

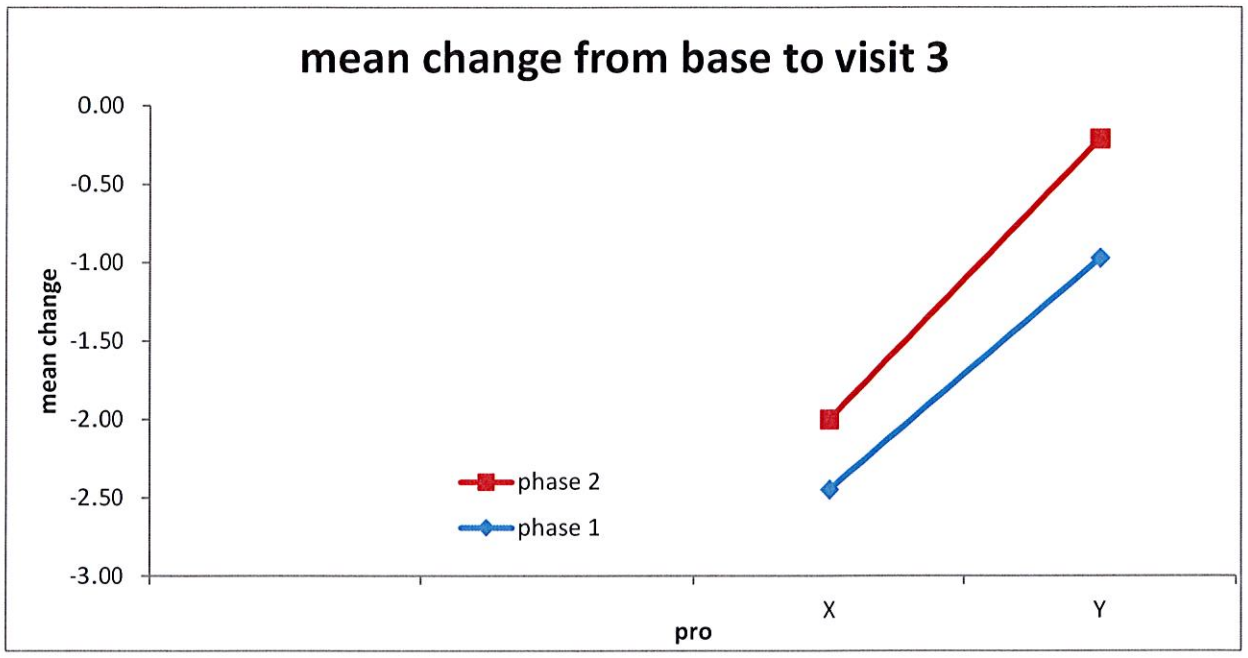

Figure 3: Organoleptic Change Scores Compared to Baseline for Groups X and Y (data from Table 10).

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FINAL CLINICAL SITE REPORT
(Report for Oral Rinses A and B)

Protocol: UHRG-RPR-Oral Rinse Malodor-ADA-2016

University Health Resources Group
5714 Canterbury Drive
Culver City, California 90230

March 2017

Title of Project:	Efficacy of ClōSYS oral rinse product in human subjects in controlling oral malodor (Oral Rinses A and B)
Protocol:	UHRG-RPR-Oral Rinse Malodor-ADA-2016
Principal Investigator:	Sushma Nachnani, MS PhD University Health Resources Group 5714 Canterbury Drive Culver City, California 90230
Study Sponsor:	Rowpar Pharmaceuticals, Inc. James L. Ratcliff, PhD. 16100 N. Greenway-Hayden Loop, Suite 400 Scottsdale, AZ 85260
Sponsor's Project Manager:	Jaiprakash G. Shewale, PhD Technical Director
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- Screening and enrollment
- Phase I treatment period (3 week)
- Washout period (2 week)
- Phase II treatment period (3 week)

Number of Exposures (Uses): Twice a day after tooth brushing, each in the morning and in the evening, with 15ml of assigned oral rinse for each subject; Off-site.

Duration of Each Exposure (Use): 30 seconds

Blinding: Double blind

Overall Duration of Study: 3 week (phase I treatment period) + 2 week (washout period) + 3 week (phase II treatment period)

Method of Patient Assignment: Randomized

Study Type: Breath Freshener Oral Rinse

Primary Efficacy Variable(s): Average (across judges) organoleptic intensity rating rated at baseline, 1 week post initiation of product use, 2 weeks post initiation of product use, and 3 weeks post initiation of product use. Average (across judges) organoleptic intensity rating rated at baseline two, 1 week post reinitiating of product use, 2 weeks post reinitiating of product use, and 3 weeks post reinitiating of product use.

Study Arms: ClōSYS Alcohol-Free Oral Rinse (ClōSYS Unflavored Oral Rinse), Placebo ClōSYS Oral Rinse Solution (Placebo Oral Rinse).

Start Date: August 2016

End Date: 01/29/2017

Status: Completed

CLINICAL SITE REPORT

Introduction

A randomized, 2-way cross-over trial was designed and conducted to evaluate the effect of ClōSYS Oral Rinse product on oral malodor.

Study Objective

The purpose of this study was to assess the efficacy of ClōSYS Unflavored Oral Rinse product (ClōSYS Alcohol-Free Oral Rinse) in human subjects in controlling oral malodor, in partial fulfillment of the requirements for recognition by the American Dental Association (ADA).

Protocol Approvals: Prior to the conduct of the study, protocols and pertinent documents were submitted to and approved by Biomed IRB, Biomedical Research Institute of America, P.O. Box 600870, San Diego, CA 92160. An informed letter of consent was reviewed and signed by each of the study participants before the initiation of the project. A copy of the signed informed letter of consent was provided to the subject. The protocol was approved by ADA.

Overall Study Design — Description

This was an *in-vivo*, eight-week, single-center, randomized, double-blind (subject/investigator), 2-way cross-over design clinical trial. Fifty adult volunteers, aged 21 to 65 years, with a slight to strong intrinsic oral malodor of at least 2.6 but no higher than 4.5 on an intensity scale of 0-5, as determined by a panel of trained odor judges, following 12-18 hours oral hygiene abstention, were enrolled. There were two groups. Each subject of each group was crossed over to the other group after the washout period. In the first phase, 25 subjects were randomly assigned to the active group; the other 25 subjects were assigned to the control group. In the second phase, the participants were crossed over to the other groups (Table 1).

Screening

Every potential subject was interviewed by the assigned staff member and was provided an Informed Consent Form (ICF). Subjects who met eligibility criteria and signed the ICF then had an Oral Screening Examination performed by a study dentist. Potential subjects who satisfied all oral examination criteria maintained eligibility.

After review of the results of the ICF, Screening Interview, and Screening Oral Examination, the Principal Investigator determined whether or not a subject was enrolled in the study. The following procedures were conducted:

- Informed Consent: The purpose and procedures of the Study were described to the subject. The subject had the opportunity to ask questions about the study in private and upon permission signed the ICF. The HIPAA form was also explained to the subject at this stage in Screening.
- Screening Interview: The subject was asked inclusion and exclusion questions, demographics, smoking or non-smoking, and date of last professional dental cleaning. A brief medical history of each subject was recorded.
- Medical History and Medications: A brief medical history of each subject was recorded.
- Dental Health History: The subject was asked to report the date of last scaling and root planing or polishing and date of last professional cleaning.
- Oral Examination: The oral cavity was evaluated for any mucosal irritation, lesions or pathology. Each evaluation included face lymph nodes, lips, buccal mucosa, hard and soft palates, oropharynx, tongue, floor of the mouth, edentulous ridges and teeth.
- To be eligible for participation in the Study, subjects had no clinical evidence of mucosal inflammation and/or lesions or other visual evidence of oral disease.

Breath Examination Instruction

Subjects were given following instructions for the baseline and subsequent weekly examination visits. Subjects abstained from all oral hygiene regimens including brushing, using mouth rinse, and cleaning their tongue for 12 hours. Subjects abstained from eating 8 hours prior to their scheduled visit and abstained from drinking at least 2 hours prior to their visit. Subjects also abstained for 12 hours from last intake of alcohol, foods containing sulfur compounds such as garlic or onion, scented cosmetics, and smoking or using any tobacco products. They had 24 hours abstention from medicated lozenges, mints, sweets or gum that contain antimicrobial agents, including but not limited to, xylitol, essential oils, cetylpyridinium chloride, chlorine dioxide, and zinc. They refrained from elective dental procedures. Subjects did not use any other oral rinse or mouthwash. Prior to breath examinations, subjects were instructed to have their mouth closed for at least 2 minutes.

Study Formulations

ClōSYS Alcohol-Free Oral Rinse (ClōSYS Unflavored Oral Rinse), Placebo ClōSYS Oral Rinse Solution (Placebo Oral Rinse). ClōSYS Unflavored Oral Rinse product containing 0.1% stabilized chlorine dioxide (sodium chlorite) in an aqueous solution was supplied by Rowpar Pharmaceuticals in 16oz. white, opaque bottles, along with measuring cups. The Study Placebo was a close match in taste and appearance to the Study Formulation but without stabilized chlorine dioxide. The formulations were labeled as Oral Rinse A and Oral Rinse B.

Inclusion Criteria

Subjects who met the following criteria were enrolled in the study:

- Had read, signed, and received a copy of the Informed Consent prior to Study initiation,
- Was able to follow verbal and/or written instructions, perform oral hygiene procedures and return to the test facility for specified Study examinations,
- Was between the ages of 21 and 65 years of age, male or female,
- Had normal oral interior cheek wall tissues,
- Was in good general health as determined by medical history and clinical judgment that no severe or debilitating disease existed that impeded participation in the Study,
- Had an average organoleptic intensity rating of at least 2.6 but maximum 4.5 on an intensity scale of 0-5.

Exclusion Criteria

Subjects were excluded from study participation where there was evidence of:

- Pregnancy or nursing per subject report,
- Diagnosis of Xerostomia, including medication induced Xeriostomia,
- Any oral or extraoral piercing that interferes with the ability to perform study procedures and/or clinical assessments in the mouth,
- Fixed or removable oral appliances, such as orthodontic brackets or retainer, partial or complete dentures,
- Advanced periodontal disease or excessive gingival recession, per Investigator/Examiner discretion,
- A known allergy or sensitivity to products used in the study,
- Unwillingness to abstain from all other oral hygiene products other than those prescribed for the duration of the study,
- Heavy deposits of calculus, either supragingival and/or subgingival, per Investigator/Examiner discretion
- A history of severe transmittable infectious disease (hepatitis, HIV, tuberculosis),
- A medical or dental condition that was unduly affected by participation in the study, per Investigator discretion,
- Any other condition that Principal Investigator considered interfering with the study,
- Smokers.

Enrollment

Each subject who completed the screening period of the study was registered or randomized and assigned a unique sequential subject identification number. This number was used to identify the subject and was used on all applicable study documentation related to that subject. The subject identification number remained constant throughout the first phase. A new subject identification number that is 100 higher than the original number was used throughout the second phase for a

statistical purpose (e.g. 201 is used as a new subject identification number of subject 101 for the second phase).

The written Informed Consent document was signed and personally dated by the subject and completed to a fully executed Informed Consent document and processed per the Institution's Standard Operating Procedures.

Before subjects were entered into the study, a copy of the written Institutional Review Board approval of the protocol, Informed Consent Form, and all other applicable subject information and/or recruitment material were on file at the Institution.

Materials

Each subject received one bottle (16oz) of either ClōSYS Unflavored Oral Rinse, or Placebo. The bottles of the respective Oral Rinse were replaced every week. Additionally, 120 measuring cups, one tube of Crest Cavity Protection Toothpaste, Regular (8.2oz) and one ClōSYS toothbrush was provided to each subject. Upon depletion of the toothpaste, an additional tube was provided. Each subject received one toothbrush once every two weeks.

Calibration of Judges

The organoleptic evaluation panel consisted of three organoleptic judges (OJs) who were trained and calibrated prior to the initiation of the study. These judges have participated in oral malodor studies for many years. We have developed a program for training organoleptic judges over the last twenty plus years that we have been involved in oral malodor clinical trials.

It is important that the individuals who serve as odor judges have a good sense of smell. This was verified by using a simple smell identification test (Sensonics Inc., Haddon Heights, NJ, USA).

The OJs completed a 4-phase training protocol based on the American Society of Testing and Materials standards (ASTM): (i) introduction to sensory scales, n-butanol reference, sniffing techniques; (ii) pretraining measurements; 20 samples of varying intensities of four unpleasant and three pleasant odorants; (iii) exercises assessing quality, intensity, ranking, and matching; and (iv) post-training measurements.

After the basic training the OJs sniffed 15 subjects to confirm that they were all calibrated.

Study Visits

Different activities for data collection at each visit are summarized in Table 2.

Baseline Visit

The initial baseline visit took place on the same day of the initial screening visit. Screening documentation was revisited and it was verified that all the data had been recorded. The oral examination was performed. A panel of trained calibrated judges assessed the breath. In order to create reproducible assessment, subjects were instructed to close their mouths and breathe through their nose for two minutes. After two minutes, the subject was instructed to count out

loud (1-20) while the subject was exhaling through the mouth. During this time, the odor judges assessed the odor intensity at approximately 10 centimeters from the subject's mouth. The judges gave an organoleptic score based on a 6-level scale described in Table 3. The subject was directed to the staff member for dispensing of the proper product according to randomization and patient log. The subject was instructed to continue with normal oral-hygiene practice during the entire study, including tooth brushing but omitting any use of oral rinses or mouthwashes other than the study products. The subject was given a calendar diary to record uses of the assigned products. Subjects were instructed to return all used and unused products each week during their visit. Subsequent study visits were scheduled at one (1), two (2), and three (3) weeks after the baseline visit. After a 2-week washout period, the subject was scheduled again one (1), two (2), and three (3) weeks after the second baseline visit.

Visit 1 – One Week Post Initiation of Product Use

This study visit took place one (1) week post initiation of subject's use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 2 confirmed.

Visit 2 – Two Weeks Post Initiation of Product Use

This study visit took place two (2) weeks post initiation of subject's use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 3 was confirmed.

Visit 3 – Three Weeks Post Initiation of Product Use

This study visit took place three (3) weeks post initiation of subject's use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The appointment date scheduled for Visit 4 was confirmed. Oral hygiene products for the washout period were dispensed.

Washout Period

Subjects had a two week "washout" period where they did not use any study materials but continued with normal oral-hygiene practices, including tooth brushing using Crest Cavity Protection Toothpaste, Regular but omitting any use of oral rinses or mouthwashes.

Baseline Two – Five Weeks Post Initiation of Product

This second baseline visit took place five (5) weeks post initiation of subject's initial use of product. Screening documentation was revisited and any new medical history on respective documents was updated. It was verified that all the data had been recorded. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for baseline one visit. The subject was directed to the staff member for dispensing of the proper product according to randomization and patient log. The subject was instructed to continue with normal oral-hygiene practice during the entire study, including tooth brushing but omitting any use of oral rinses or mouthwashes other than the study products. The subject was given a calendar diary to record uses of the assigned product. The subject was instructed to return all used and unused products. The appointment date scheduled for Visit 5 was confirmed.

Visit 5 – One Week Post Reinitiation of Product Use

This study visit took place one (1) week post reinitiation of subject's restart of use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 6 was confirmed.

Visit 6 – Two Weeks Post Reinitiation of Product Use

This study visit took place two (2) weeks post reinitiation of subject's restart of use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product. The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded. The subject was directed to the staff member for dispensing of additional oral rinse. The appointment date scheduled for Visit 7 was confirmed.

Visit 7 – Three Weeks Post Reinitiation of Product Use

This study visit took place three (3) weeks post reinitiation of subject's restart of use of product. The subject's unused product was collected to be measured and recorded along with the patient diary. The subject returned all used and unused products and was given a new bottle of product.

The subject was asked of any changes that occurred in the medical or dental health since the last visit. The same oral examination and organoleptic evaluation were performed using the same method and procedure described for the baseline visit. It was verified that all the data had been recorded.

Results and Discussion

None of the 23 enrolled subjects in group A dropped during Phase I of the study. However, 1 subject in group A dropped in Phase II. Of the 25 enrolled subjects in group B, 24 and 22 completed Phase I and Phase II of the study, respectively. Major reasons for withdrawal were commuting and scheduling issues.

There were no adverse events reported by subjects within the duration of the study.
Oral soft tissue examinations found no evidence of anomalies of soft and hard palate, buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands, and the tonsilar and pharyngeal areas in any of the subjects before and after the use of test products during each phase.

The distribution of gender, age, and race of subjects enrolled in the study is summarized in Tables 4, 5, and 6. The assignment of a subject to a group was based on randomization table and sequential to enrolment. Nonetheless, representation from both genders, over the target span of age, and different races was present in the study.

Organoleptic scores of each group and at each visit were recorded for both Phases I and II. The raw data was processed for statistical distribution. The values for mean, standard deviation (SD), and standard error of the mean (SEM) are presented in Tables 7 and 8. The results are also summarized in Figure 1. The mean values for organoleptic score for the two groups at the respective baselines were not significantly different; mean organoleptic score for groups A and B at the baseline of Phase I were 3.58 and 3.65 and at Phase II were 3.28 and 3.21, respectively. The mean organoleptic score for group B decreased at a much more rapid rate during each visit compared to group A. Mean organoleptic score in Phase I dropped from 3.65 at baseline to 1.40 at visit 3 in group B and from 3.58 at baseline to 2.30 at visit 3 in group A. Similarly, mean organoleptic score in Phase II dropped from 3.21 at baseline to 1.34 at visit 3 in group B and from 3.28 at baseline to 2.90 at visit 3 in group A. Importantly, the observation of Phase I was reproducible in Phase II after the crossover. The SEM values for all data points in Phase I and Phase II were between 0.08 and 0.16 exhibiting minimal variation in the distribution of the data.

The analysis was also performed by pooling the organoleptic scores from Phase I and II for each group. The results are summarized in Table 9 and Figure 2. Mean organoleptic score dropped from 3.43 at baseline to 1.37 at visit 3 in group B and from 3.43 at baseline to 2.60 at visit 3 in group A. The pooled SEM values for all data points were 0.08 exhibiting minimal variation in the distribution of the data.

Net reduction in oral malodor is the difference in organoleptic score at baseline and visit 3. Change in organoleptic score at visit 3 compared to organoleptic score at respective baseline was calculated for each group and for Phase I and II. The results are presented in Table 10 and Figure 3. Oral Rinse B decreased the mean organoleptic score by 2.250 and 1.877 in Phase I and II

respectively. Whereas, Oral Rinse A decreased the mean organoleptic score only by 1.275 and 0.367 in Phase I and II, respectively.

Mean difference, Standard Error (SE) difference, and *p*-values at each visit for Oral Rinses B vs. A for Phase I and II are summarized in Tables 11 and 12. It is evident that Oral Rinse B exhibited statistically significant reduction of oral malodor compared to Oral Rinse A.

Label Key

Rowpar Pharmaceuticals, Inc. released the label key after completion of the study and data analysis. The products were labeled as follows:

- ClōSYS Placebo Oral Rinse was labeled as Oral Rinse A
- ClōSYS Unflavored Oral Rinse was labeled as Oral Rinse B

Conclusions

The data presented in Tables 7 to 12 and Figures 1 to 3 and the label key support the following conclusions:

1. ClōSYS Unflavored and Placebo Oral Rinses tested in this study do not exhibit any adverse effects and therefore are safe to oral tissues.
2. The use of ClōSYS Unflavored Oral Rinse twice daily for up to three weeks provides statistically significant reduction in oral malodor compared to the reduction in oral malodor by placebo.
3. The use of ClōSYS Placebo Oral Rinse twice daily for up to three weeks provides statistically less reduction in oral malodor compared to the reduction in oral malodor by ClōSYS Unflavored Oral Rinse.

Table 1. Study Design

Group	Product	Number of Subjects	Description
A, B	ClōSYS Unflavored Oral Rinse(CUOR) & Placebo Oral Rinse	50 subjects randomly assigned to two groups	25 subjects will start with the CUOR, observe washout period, and switch to Placebo.
			25 subjects will start with the Placebo, observe washout period, and switch to CUOR.

Table 2. Data Collection Schedule and Visits

Procedures	Phase I Visit				Washout	Phase II Cross-over Visit			
	Base-line 1	1	2	3	2-week	Base-line 2	6	7	8
Screening Documentation	X					X			
Oral Examination	X	X	X	X		X	X	X	X
Health Changes		X	X	X			X	X	X
Malodor Level	X	X	X	X		X	X	X	X
Data Recorded	X	X	X	X		X	X	X	X
Product & Log Dispensed	X	X	X			X	X	X	
Unused Product & Log Collected		X	X	X		X	X	X	X
Follow-Up Visit Scheduled	X	X	X	X		X	X	X	
Oral Hygiene Instructions Given	X					X			

Table 3. American Dental Association Organoleptic Intensity Rating

ADA Organoleptic Intensity	
Rating	**Odor Intensity**
0	Malodor cannot be detected
1	Questionable malodor, barely detectable
2	Slight malodor, exceeds the threshold of malodor recognition
3	Malodor is definitely detected
4	Strong malodor
5	Very strong malodor

Table 4. Gender Distribution within Study Groups

Group	Female		Male		Total Number
	Number	%	Number	%	
A	18	78.3	5	21.7	23
B	14	56.0	11	44.0	25

Table 5. Age Distribution in Years within Study Groups

Group	Minimum	Maximum	Median	Mean	SD	SEM
A	21	64	40	40.83	15.81	3.30
B	21	65	42	41.16	14.95	2.99

Table 6. Ethnicity Distribution within Study Groups

Ethnicity	A		B	
	Number	%	Number	%
Asian Oriental	1	4.3	1	4.0
Caucasian	4	17.4	4	16.0
Hispanic	16	69.6	16	64.0
Asian Indian	1	4.3	1	4.0
Multi-Racial	1	4.3	3	12.0
Total	23	100	25	100

Table 7. Malodor Mean Values for Phase I

Group (n)	Baseline -1			Visit-1			Visit-2			Visit-3		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
A (23)	3.58	0.67	0.14	2.93	0.40	0.08	2.39	0.61	0.13	2.30	0.67	0.14
B (24)	3.65	0.66	0.13	2.29	0.65	0.13	1.81	0.58	0.12	1.40	0.61	0.13

Table 8. Malodor Mean Values for Phase II

Group (n)	Baseline -2			Visit-1			Visit-2			Visit-3		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
A (22)	3.28	0.52	0.11	3.00	0.35	0.08	2.91	0.35	0.07	2.90	0.35	0.08
B (22)	3.21	0.52	0.11	2.08	0.74	0.16	1.47	0.63	0.14	1.34	0.60	0.13

Table 9. Malodor Mean Values for Phase I and Phase II Combined

Group	Baseline		Visit-1		Visit-2		Visit-3	
	Mean	Pooled SEM	Mean	Pooled SEM	Mean	Pooled SEM	Mean	Pooled SEM
A	3.43	0.08	2.96	0.08	2.65	0.08	2.60	0.08
B	3.43	0.08	2.19	0.08	1.64	0.08	1.37	0.08

Table 10: Organoleptic Change Scores Compared to Baseline in Phase-I and Phase-II

Group	Phase-I					Phase-II				
	n	Mean	SD	SEM	p-value*	n	Mean	SD	SEM	p-value*
A	23	-1.275	0.808	0.168	**0.196×10^{-12}**	22	-0.367	0.464	0.099	**0.0157**
B	24	-2.250	1.041	0.212	**0.998×10^{-26}**	22	-1.877	0.638	0.136	**0.542×10^{-20}**

*p-values for change of the mean from respective baseline

Table 11: Mean differences, Standard Error difference, and *p*-value for Oral Rinses A and B at each visit during Phase I

Visit	Mean difference	SE difference	p-value
Baseline	0.073	0.162	0.6532
1	-0.636	0.162	0.0001
2	-0.582	0.162	0.0004
3	-0.902	0.162	0.1131×10^{-6}

Table 12: Mean differences, Standard Error difference, and *p*-value for Oral Rinses A and B at each visit during Phase II

Visit	Mean difference	SE difference	p-value
Baseline	-0.064	0.167	0.7027
1	-0.924	0.167	0.1195×10^{-6}
2	-1.439	0.167	0.5648×10^{-14}
3	-1.564	0.167	0.6121×10^{-16}

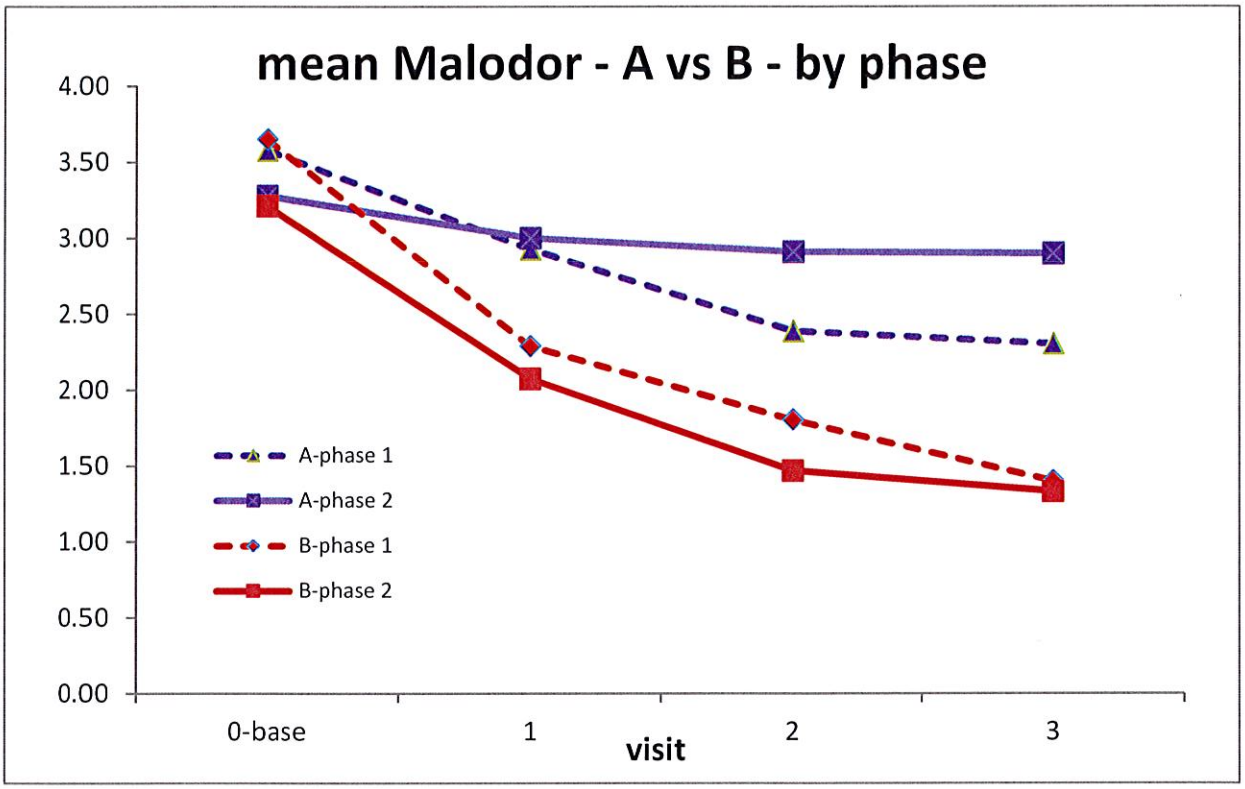

Figure 1. Trend in Mean Malodor for Groups A and B for Individual Phases (data from Table 7 and Table 8).

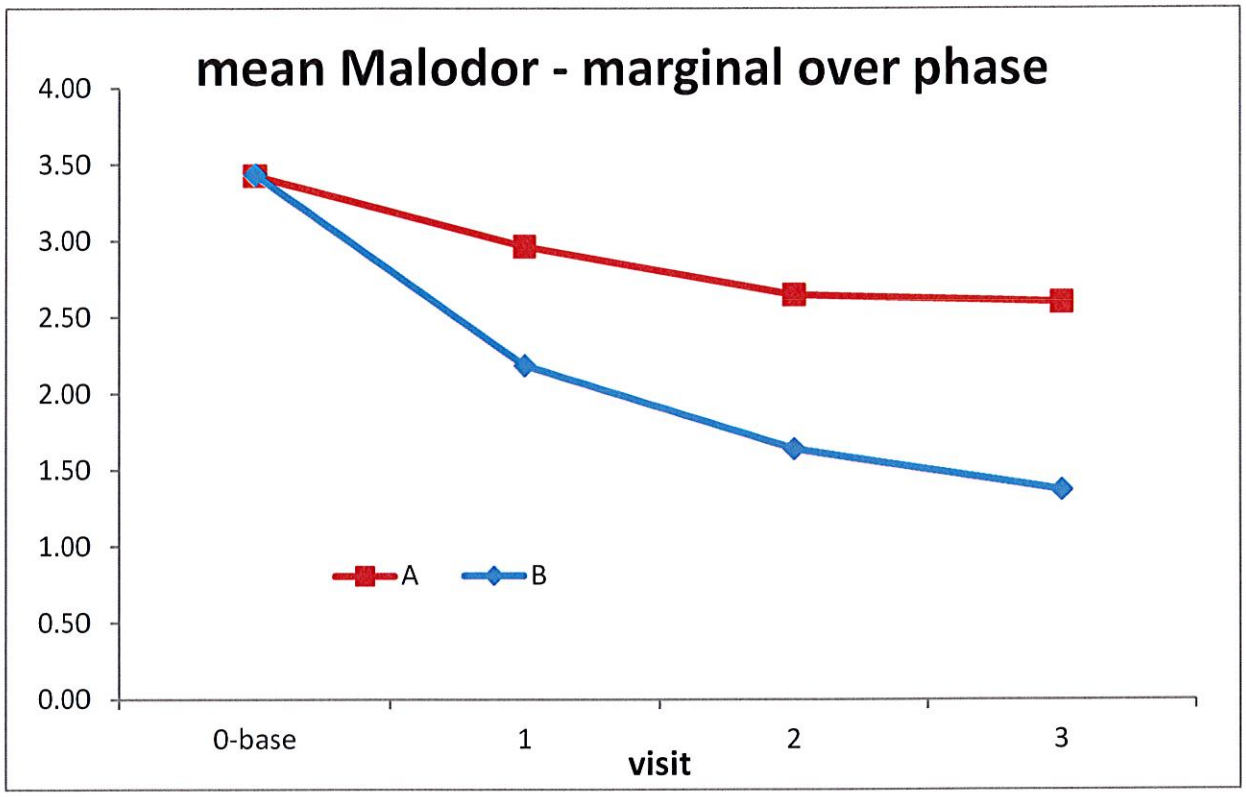

Figure 2. Trend in Combined Mean Malodor for the Two Phases for Groups A and B (data from Table 9).

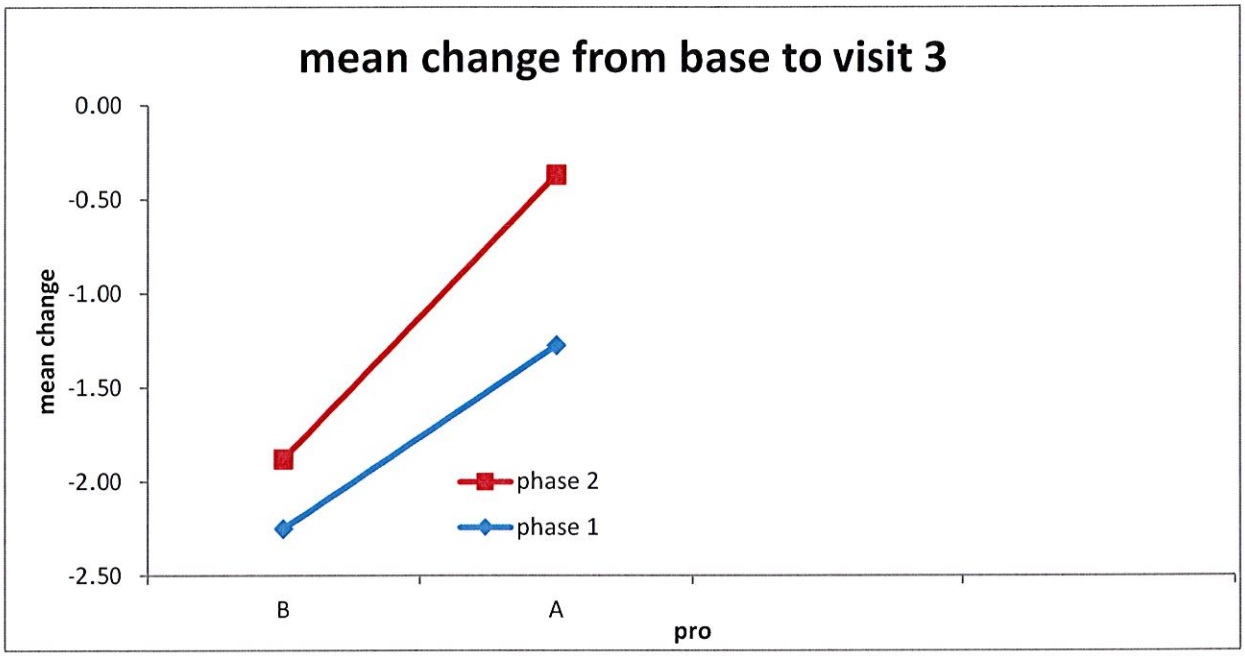

Figure 3: Organoleptic Change Scores Compared to Baseline for Groups A and B (data from Table 10).