1 SYNOPSIS

Name of Sponsor/Company McNeil Consumer & Specialty Pharmaceuticals ***Name of Finished Product:*** NA ***Name of Active Ingredient:*** Benzydamine HCl	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: A Double-Blind, Randomized, Vehicle-Controlled Study Comparing the Safety and Efficacy of Benzydamine Hydrochloride 0.15% Oral Rinse Including a Separate Open-Label Standard of Care Arm in Subjects With Radiation-Induced Oral Mucositis

Investigators: The 75 investigators are listed in Appendix 14.1.4.

Study Centers: The 75 investigational sites are listed in Appendix 14.1.4.

Publication (reference): None

Study Period: ***Phase of Development:*** 2/3
Date of first subject enrolled: December 4, 2002
Date of notification of study termination: December 15, 2004
Date of last study medication taken by subject: December 19, 2004
Date of last subject completed: March 8, 2005

Objectives: The objectives of the study were to compare the efficacy and safety of benzydamine 0.15% oral rinse to vehicle oral rinse in the treatment of radiation-induced oral mucositis, and to compare Standard of Care to vehicle oral rinse to ensure that the vehicle did not have detrimental effects on the oral mucosa.

Methodology: This was a multicenter, double-blind, randomized, vehicle-controlled, parallel study including an open-label Standard of Care arm. This study was conducted in 605 subjects. Subjects who were likely to develop oral and/or oropharyngeal mucositis related to head and neck radiation were candidates for this study. Eligible subjects were stratified according to center and treatment regimen (ie, radiation alone or radiation therapy [RT] combined with concomitant chemotherapy). Subjects were randomly assigned in a 2:2:1 ratio to either benzydamine 0.15% oral rinse, vehicle oral rinse, or Standard of Care. Following an oral examination, study medication for those subjects randomized to receive a double-blind oral rinse was initiated prior to the start of RT. Double-blind oral rinses were continued daily throughout the duration of radiation treatment and for two weeks after completion of the RT regimen.

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Subjects randomized to the open-label Standard of Care arm did not receive benzydamine 0.15% oral rinse or vehicle oral rinse, but were instructed to follow the same oral hygiene guidelines that were provided to all other study participants. These guidelines represent the current Standard of Care. These same subjects were required to adhere to the same study procedures that the other study participants followed. They were permitted to roll over and receive benzydamine 0.15% oral rinse in an open-label phase if a World Health Organization (WHO) mucositis score of 3 or more was reached. They were required to continue to follow all study procedures at that time.

Oral examinations and food intake questionnaires were performed for each subject three times a week for the duration of RT. WHO mucositis scores were derived based on two components: the evaluator's oral examination assessments and the subject's response to the food intake questionnaires. Quality of life assessments (University of Washington Quality of Life Questionnaire) were performed once a week for the duration of RT. Changes to concomitant medications and any adverse events experienced were recorded at each study visit (ie, three times weekly at time of food intake assessments).

A diary was given to each subject to record the date and time of study medication administration (if applicable) and the administration of any analgesics to alleviate pain or discomfort associated with oral mucositis, including medication name, strength, and time of the dose. In addition, subjects were asked to record their oral hygiene care (ie, tooth brushing, flossing) in their diaries.

Interim Analysis: An interim analysis was conducted when approximately half (n=381) of the planned 750 subjects had completed the study. A Data Monitoring Committee (DMC) reviewed the results of the interim analysis. Based on the results of the interim analysis and the recommendations of the DMC, the study was stopped.

Number of Subjects (planned and analyzed): This study was designed for the enrollment of 750 subjects (300 subjects in the benzydamine 0.15% oral rinse group, 300 subjects in the vehicle oral rinse group, and 150 subjects in the Standard of Care group). Data were available for 605 subjects who were enrolled in this study (251 subjects in the benzydamine 0.15% oral rinse group, 242 subjects in the vehicle oral rinse group, and 112 subjects in the Standard of Care arm).

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Diagnosis and Main Criteria for Inclusion:
Diagnosis of pathologically confirmed head and neck malignancy involving one or more of the following sites: oral cavity, oropharynx extending down to the level of the supraglottic area, nasopharynx, maxillary sinus and parotid gland. Subjects were included who were scheduled to receive a continuous course (eg, often six to eight weeks) of conventional or hyperfractionated external beam radiation for cancer of the head and neck region with or without chemotherapy. In addition, at least two oral tissue sites (not including areas of previous lesions, tumor, surgical resection, or the lips) must have been included in the RT treatment volume and planned to receive a total radiation dose of 5500 cGy or higher, given in a single daily fraction of 180 to 220 cGy or twice daily fractions of 110 to 150 cGy.

Test Product, Dose and Mode of Administration, Batch Number: The test product was benzydamine 0.15% as a nonsterile oral rinse. Subjects were instructed to rinse their mouths with water before using the study medication to eliminate any food particles or debris. The directions for the oral rinse were to place 15 milliliters (mL) in mouth for two minutes, gargling for a few seconds at the beginning and end of the rinse, and then to expectorate the entire dose. Dosing was every two to three hours while awake for a minimum of four times daily to a maximum of eight times per day. Batch number: SLAX-C.

Reference Product, Dose and Mode of Administration, Batch Number: The reference product was vehicle oral rinse as a nonsterile solution. The vehicle oral rinse excipients included alcohol, menthol, glycerin, other flavoring agents, and preservatives. Subjects were instructed to rinse their mouths with water before using the study medication to eliminate any food particles or debris. The directions for the oral rinse were to place 15 mL in mouth for two minutes, gargling for a few seconds at the beginning and end of the rinse, and then to expectorate the entire dose. Dosing was every two to three hours while awake for a minimum of four times daily to a maximum of eight times per day. Batch number: SLAW-C.

Standard of Care Study Group: Subjects randomized to the open-label Standard of Care arm were instructed to follow the same oral hygiene guidelines that were provided to all other study participants. They were also required to adhere to the same study procedures that the other study participants followed. These subjects were permitted to roll over and receive benzydamine 0.15% oral rinse in an open-label phase if a WHO mucositis score of 3 or more was reached. They were required to continue to follow all study procedures at that time.

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Duration of Treatment: The duration of study participation was to extend through each subject's course of RT (eg, often six to eight weeks) plus two weeks following completion of RT. Dosing with the double-blind oral rinses was to begin prior to the initiation of RT. Efficacy data were collected throughout the prescribed RT period. Safety data were collected throughout the subject's prescribed course of radiation and for an additional two weeks following completion of radiation.

Criteria for Evaluation:

Efficacy: The primary endpoint to demonstrate efficacy of benzydamine 0.15% oral rinse compared with vehicle oral rinse and the noninferiority of vehicle compared with Standard of Care, was the cumulative proportion of subjects with severe mucositis (WHO mucositis score of at least 3) at a cumulative radiation dose of 5500 cGy.

The secondary endpoints were the following: cumulative RT to first use of an opioid for oral mucositis, cumulative RT to first ulceration, and cumulative RT to first RT suspension due to oral mucositis. Quality of life measurements (University of Washington Quality of Life Questionnaire) were also evaluated.

Safety: Safety assessments consisted of routine physical examinations and oral examinations, an evaluation of reported adverse events, laboratory determinations, vital signs, and body weight throughout the study.

Statistical Methods:

The intent-to-treat (ITT) population was used for the primary efficacy analysis. Comparability between groups on demographic and baseline variables was performed using a one-way ANOVA for continuous variables and Fisher's Exact test for categorical variables.

Interim Analysis:

An interim analysis was conducted when approximately half of the anticipated total number of subjects had completed the study. The interim analysis did not demonstrate efficacy for the benzydamine 0.15% oral rinse group compared with the vehicle group and showed a low probability of success if the trial were to continue to the planned completion. An imbalance in the number of deaths, serious adverse events, and number of subject withdrawals due to adverse events was also shown. Based upon the results of the interim analysis and the recommendation of the DMC, the study was stopped.

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Efficacy Analysis:
Two independent comparisons were of interest for the primary efficacy variable of cumulative proportion of subjects with severe mucositis (WHO mucositis score of at least 3) at a cumulative radiation dose of 5500 cGy: the comparison of benzydamine 0.15% oral rinse to vehicle oral rinse and the comparison of vehicle with Standard of Care. Vehicle oral rinse and Standard of Care were compared for efficacy on this variable only. The superiority of benzydamine 0.15% oral rinse to vehicle oral rinse was evaluated with a Cochran-Mantel-Haenszel test of general association stratified by center and treatment regimen (radiation alone or chemotherapy plus radiation). Noninferiority of vehicle oral rinse to Standard of Care was evaluated with a one-sided 97.5% confidence limit of the difference in proportion of subjects with a WHO mucositis score of at least 3 at 5500 cGy. The 97.5% confidence limit for the difference in proportions had to have been less than 0.15 to declare noninferiority of vehicle to Standard of Care. In addition, success rates of the primary endpoint were estimated and compared using the Kaplan-Meier (K-M) survival curves of cumulative RT to first occurrence of a WHO mucositis score of 3 at the single point of 5500 cGy using Greenwood's estimate of the variance. The 97.5% confidence limit for the difference in the K-M estimates at 5500 cGy had to have been less than 0.15 to declare noninferiority of vehicle to Standard of Care. In the final report, a confidence limit of 97.6% was used to adjust for the interim analysis in both sets of analyses comparing vehicle with Standard of Care.

For the secondary endpoint of cumulative RT to first use of an opioid for oral mucositis, the use of systemic analgesics was classified into two levels: non-opioid and opioid. The distribution of cumulative radiation dose to the first use of an opioid for oral pain associated with radiation-induced oral mucositis was compared between treatments by survival analysis. Survival curves were compared with the log-rank test. Subjects who discontinued RT or double-blind oral rinse before using an opioid were right censored at the cumulative radiation dose at discontinuation. Subjects who never used an opioid were right censored at the cumulative radiation dose at the end of their radiation treatment. Opioid use after the end of radiation treatment was included in the analysis. Similar analyses were conducted for the secondary endpoints of cumulative RT to first ulceration and cumulative RT to first RT suspension due to oral mucositis.

Quality of life measurements (University of Washington Quality of Life Questionnaire) were an additional endpoint. The average total score of all categories in the quality of life scale were tabulated and presented graphically by treatment group and week. Change from screening was also tabulated overall and by week. The average score for each question

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was tabulated by treatment group at screening, at the final visit, and change from screening. These changes were compared between the benzydamine 0.15% oral rinse and vehicle oral rinse groups using an analysis of covariance with the screening quality of life scores as a covariate.

Safety Analysis:
Adverse events were tabulated by treatment. There were four groups summarized: benzydamine 0.15% oral rinse, vehicle oral rinse, Standard of Care before rollover, and Standard of Care after rollover to open-label benzydamine 0.15% oral rinse. Since it was expected that many adverse events would be related to oncology treatment regimen and cumulative RT, adverse events were also presented for those subjects with and without concomitant chemotherapy and, separately, by cumulative RT. Summaries included the number and percent of subjects reporting adverse events, serious adverse events other than death, deaths, and subjects discontinuing due to adverse events. Adverse event rates were compared among groups using Fisher's Exact test. Adverse events were also further summarized by system organ class and MedDRA preferred term, relatedness to drug, intensity, and demographic subgroup. Changes in laboratory data, weight, and vital signs were tabulated by treatment group.

Efficacy Results:
A total of 605 subjects were enrolled in this study (251 subjects in the benzydamine oral rinse group, 242 subjects in the vehicle oral rinse group, and 112 subjects in the Standard of Care group). The three treatment groups were well balanced with respect to demographic and baseline disease characteristics. Overall, the average age was 56.9 y and consisted of 72.9% males and 78.5% Caucasians. The rate of withdrawal from the study was similar in in the benzydamine 0.15% group (29.1%) and the vehicle group (26.9%) and higher in these two groups than in the Standard of Care group (14.3%). It should be noted that a total of 68 (61%) subjects in the Standard of Care group had a deterioration in their mucositis to a WHO mucositis score of 3 leading to a planned roll over to open-label benzydamine 0.15% oral rinse. The ITT population was defined as those subjects who were randomized and dispensed double-blind oral rinse or who were randomized to the Standard of Care arm. The ITT population included 600 subjects (247 in the benzydamine 0.15% group, 241 in the vehicle group, and 112 in the Standard of Care group).

Tables 1 and 2 summarize the primary efficacy endpoint. The primary efficacy endpoint showed no statistically significant difference between the benzydamine 0.15% oral rinse

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group and the vehicle oral rinse group. The vehicle oral rinse group was noninferior to Standard of Care.

Table 1. Treatment Outcome at Primary Endpoint - Benzydamine 0.15% Versus Vehicle Oral Rinse (Intent-to-Treat)

Outcome	BZD 0.15% (N=247) n (%)	Vehicle (N=241) n (%)	p-Value[a]	p-Value[b]
N Subjects Included[c]	234	225		
Treatment Success[d]	55 (23.5)	53 (23.6)	0.824	0.998
Treatment Failure	179 (76.5)	172 (76.4)		

a: CMH test with center, oncology treatment regimen (RT or RT plus chemotherapy), treatment and outcome. From logistic regression with center, treatment and center x treatment interaction and outcome, significance of interaction term p-value = 0.848.

b: CMH test with oncology treatment regimen (RT or RT plus chemotherapy), treatment and outcome.

c: Subjects who were withdrawn due to study termination by sponsor are not included as success or failure unless they received at least 5500 cGy.

d: Success defined as reaching 5500 cGy without having a WHO mucositis score of 3 or more and adjusted as per the protocol to take into account the potential effects of subject dropouts.

Table 2. Treatment Outcome at Primary Endpoint - Vehicle Oral Rinse Versus Standard of Care (Intent-to-Treat)

Outcome	Vehicle (N=241) n (%)	Std of Care (N=112) n (%)	Difference in proportion of successes[a]	Upper one sided 97.6% confidence limit of difference in proportion of successes[b]
N Subjects Included[c]	225	103		
Treatment Success[d]	54 (24.0)	19 (18.4)	-0.056	0.042
Treatment Failure	171 (76.0)	84 (81.6)		

a: Logistic regression with center, treatment and center x treatment interaction and outcome, significance of interaction term p-value = 0.916.

b: Upper confidence limit in difference in success rates (Standard of Care - Vehicle) has to be less than 0.15. Limit of 97.6% used because 0.5% spent in interim analysis.

c: Subjects who were withdrawn due to study termination by sponsor are not included as success or failure unless they received at least 5500 cGy.

d: Success defined as reaching 5500 cGy without having a WHO mucositis score of 3 or more and adjusted as per the protocol to take into account the potential effects of subject dropouts.

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Table 3 summarizes the results for secondary efficacy measures. The secondary efficacy endpoints showed no statistically significant differences between the benzydamine 0.15% oral rinse group and the vehicle oral rinse group.

Table 3: Kaplan-Meier Survival Curve Estimates and Comparison of Benzydamine 0.15% and Vehicle at 5500 cGy

Secondary endpoint[a]	BZD 0.15% (N=247)	Vehicle (N=241)	p-Value[b]
First use of an opioid for oral mucositis	36.9%	31.8%	0.284
First ulceration due to oral mucositis	3.3%	5.6%	0.309
First RT suspension due to oral mucositis	96.7%	94.6%	0.119

a: Survival defined as not yet having the endpoint
b: Log Rank sum test of outcome by treatment

The deterioration in quality of life total scores was significantly (p=0.045) less in the benzydamine 0.15% oral rinse group (mean change of –77.9) from screening to the final visit compared with the vehicle oral rinse group (mean change of –97.4).

Safety Results:
All study medications were relatively well tolerated, and no clinically important safety issues were identified. Many of the adverse events observed across treatment groups reflect the disease state of the subjects and the oncology treatments they were undergoing. The Standard of Care group participated in the randomized phase of the study for a shorter duration than the benzydamine 0.15% oral rinse or vehicle oral rinse groups, since 68 (61%) subjects assigned to Standard of Care attained a WHO mucositis score of 3 or more and rolled over to the open-label benzydamine phase of the study. This difference in time in the randomized phase, in addition to no study-defined drug treatment and the open-label design of the Standard of Care group, most likely contributed to the lower incidence of adverse events in the Standard of Care group. As such, the most appropriate comparisons of the incidence of adverse events were between the benzydamine 0.15% oral rinse and vehicle oral rinse groups.

Subjects in the benzydamine 0.15% oral rinse group were slightly sicker at entry compared to the other two treatment groups as indicated by three parameters. First, the benzydamine 0.15% oral rinse group had a slightly higher percentage of subjects with a tumor staging of T4 (18.6%) compared to 15.8% (vehicle oral rinse group) and 15.2% (Standard of Care group). Secondly, a slightly higher percentage of subjects in the benzydamine 0.15% oral

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rinse group were receiving RT with chemotherapy (45.7%) compared to vehicle oral rinse (44.0%) or Standard of Care (41.4%). Lastly, the mean number of chemotherapeutic agents used per subject who received chemotherapy was slightly higher in the benzydamine 0.15% oral rinse group (1.5) compared to vehicle oral rinse (1.4) or Standard of Care (1.3).

While most subjects in all treatment groups reported adverse events, there were statistically significant differences among the three treatment groups. Adverse events were reported by similar percentages of subjects in the benzydamine 0.15% oral rinse group (98.4%) and in the vehicle oral rinse group (98.8%) with no significant difference between them, compared with 94.6% of the subjects in the Standard of Care group ($p = 0.05$ for comparison of all three treatments). Drug-related adverse events (including adverse events with relation to drug of certain, probable/likely, possible, or unknown) were reported by similar percentages of subjects in the benzydamine 0.15% oral rinse group (32.4%) and in the vehicle oral rinse group (32.8%), compared with 9.0% of the subjects in the Standard of Care group ($p < 0.001$ for comparison of all three treatments). This statistically significant difference was not unexpected since the Standard of Care group was an open-label group without any study-defined drug treatment; drug-related adverse events should have been nonexistent in this group.

Serious adverse events were reported by similar percentages of subjects in the benzydamine 0.15% oral rinse group (27.9%) and in the vehicle oral rinse group (22.8%) with no significant difference between them, compared with 13.5% of the subjects in the Standard of Care group ($p = 0.010$ for comparison of all three treatments). Discontinuations due to adverse events were reported by similar percentages of subjects in the benzydamine 0.15% oral rinse group (11.7%) and in the vehicle oral rinse group (8.7%) with no significant difference between them, compared with 0% of the subjects in the Standard of Care group ($p < 0.001$ for comparison of all three treatments). The statistically significant differences observed with both the serious adverse events and the discontinuations due to adverse events were not unexpected since the Standard of Care group was an open-label group without any study-defined drug treatment.

Twelve deaths were reported during the randomized phase of the study, eight in the benzydamine 0.15% oral rinse group, four in the vehicle oral rinse group, and none in the Standard of Care group. Additionally, two deaths occurred among the subjects in the Standard of Care group after they rolled over to open-label benzydamine treatment. The difference in the death rate among treatment groups was not statistically significant. None of the deaths were considered related to study treatment. From the data reviewed at the interim analysis, the DMC concluded that there were no obvious clinical or statistical trends

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in safety that would explain the difference in mortality observed between the benzydamine 0.15% oral rinse and vehicle oral rinse treatments.

There were no clinically important differences among treatment groups for laboratory values or vital signs.

Conclusions:

- The interim analysis (n=381) did not demonstrate efficacy for the benzydamine 0.15% oral rinse group compared with the vehicle oral rinse group and showed a low probability of success if the trial were to continue to the planned completion. An imbalance in the number of deaths, serious adverse events, and number of subject withdrawals due to adverse events was also shown. Based upon the results of the interim analysis and the recommendation of the DMC, the study was stopped.

The following conclusions are based on results from the entire study cohort (n=605):

- In subjects undergoing radiation therapy, with or without chemotherapy, for tumors of the head and neck, no statistically significant difference was found between benzydamine 0.15% oral rinse and vehicle oral rinse for the primary efficacy endpoint of the cumulative proportion of subjects with severe mucositis (WHO mucositis score of at least 3) at a cumulative radiation dose of 5500 centigray.

- Vehicle oral rinse was found to be noninferior to Standard of Care treatment for the primary efficacy endpoint of the cumulative proportion of subjects with severe mucositis (WHO mucositis score of at least 3) at a cumulative radiation dose of 5500 centigray.

- Analysis of the primary efficacy endpoint by oncology regimen (RT only or RT combined with chemotherapy) showed no statistically significant differences between benzydamine 0.15% oral rinse and vehicle oral rinse in either regimen. However, in the RT only group, benzydamine 0.15% oral rinse had a survival rate 18 to 26 percentage points greater than the Standard of Care group after subjects reached a cumulative RT dose of 3000 centigray.

- Analysis of secondary efficacy endpoints showed no statistically significant differences between benzydamine 0.15% oral rinse and vehicle oral rinse with respect to cumulative RT to first use of an opioid for oral mucositis, first ulceration due to oral mucositis, or first RT suspension due to oral mucositis.

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- The deterioration in quality of life total scores was significantly (p=0.045) less in the benzydamine 0.15% oral rinse group (mean change of –77.9) from screening to the final visit compared with the vehicle oral rinse group (mean change of –97.4).

- Subjects in the benzydamine 0.15% oral rinse group were slightly sicker at entry compared to the other two treatment groups as indicated by this group having a slightly higher percentage of subjects with a tumor staging of T4, a slightly higher percentage of subjects receiving RT with chemotherapy, and a slightly higher mean number of chemotherapeutic agents used per subject who received chemotherapy.

- Many of the adverse events observed across treatment groups reflect the disease state of the subjects and the oncology treatments they were undergoing. Benzydamine 0.15% oral rinse and vehicle oral rinse groups had similar rates of adverse events, drug-related adverse events, serious adverse events, discontinuations due to adverse events, and deaths with no statistically significant differences observed. Event rates were lower with Standard of Care and were most likely due to the shorter duration of time in the randomized phase for the Standard of Care subjects, the open-label design of the Standard of Care group, and that there was no study-defined drug treatment for the Standard of Care group.

Date of the report: December 13, 2005

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