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CLINICAL INVESTIGATION

OPEN-LABEL, LONG-TERM SAFETY STUDY OF CEVIMELINE IN THE TREATMENT OF POSTIRRADIATION XEROSTOMIA

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Purpose: To assess the safety of long-term cevimeline treatment of radiation-induced xerostomia in patients with head-and-neck cancer; and to assess the efficacy of cevimeline in these patients.

Methods and Materials: A total of 255 adults with head-and-neck cancer who had received more than 40 Gy of radiation 4 months or more before entry and had clinically significant salivary gland dysfunction received cevimeline hydrochloride 45 mg t.i.d. orally for 52 weeks. Adverse events (AEs), their severity, and their relationship to the study medication were assessed by each investigator. The efficacy assessment was based on subjects' global evaluation of oral dryness on a scale of 0 (none) to 3 (severe).

Results: Overall, 175 subjects (68.6%) experienced expected treatment-related AEs, most mild to moderate. The most frequent was increased sweating (47.5%), followed by dyspepsia (9.4%), nausea (8.2%), and diarrhea (6.3%). Fifteen subjects (5.9%) experienced Grade 3 treatment-related AEs, of which the most frequent was increased sweating. Eighteen subjects (7.1%) reported at least one serious AE, and 45 subjects (17.6%) discontinued study medication because of an AE. The global efficacy evaluation at the last study visit showed that cevimeline improved dry mouth in most subjects (59.2%). Significant improvement was seen at each study visit in the mean change from baseline of the numeric global evaluation score ($p < 0.0001$).

Conclusions: Cevimeline 45 mg t.i.d. was generally well tolerated over a period of 52 weeks in subjects with xerostomia secondary to radiotherapy for cancer in the head-and-neck region. © 2007 Elsevier Inc.

Cevimeline, Xerostomia, Radiation, Head-and-neck tumor, Pilocarpine.

INTRODUCTION

According to the National Cancer Institute, approximately 3–5% of all cancers in the United States are cancers of the head-and-neck region. Such cancers affected an estimated 39,000 patients in 2005 (1). The treatment of head-and-neck cancer is multidisciplinary; it typically includes the use of radiotherapy and surgery, and chemotherapy may be an option as well (2). Through a still-speculative and

evidently complex mechanism or mechanisms, the salivary glands are very radiosensitive and especially vulnerable to both early and delayed radiation-induced injury (3–5). Radiation-induced damage to the salivary glands results in diminished saliva production and xerostomia, which is often severe and generally irreversible (3–7). In addition to the decrease in salivary volume, a decrease in the pH of saliva, an increase in its viscosity, and alterations of its electrolyte and

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immunoglobulin levels predispose patients with postirradiation xerostomia to rapidly progressing dental caries and an increased incidence of periodontal disease (7), as well as opportunistic infections by organisms such as *Candida albicans* (8, 9). Chronic hyposalivation can also lead to taste alterations (10) and difficulty with chewing, swallowing (11), and speaking (12). These changes can significantly impair the quality of life of patients with radiation-induced xerostomia (13, 14) and compromise their cancer treatment.

Saliva substitutes (15) are helpful to provide temporary symptomatic palliation of xerostomia, but their short duration of effect, unpleasant taste, and cost may limit their long-term utility; many patients prefer to use water (16). For patients with residual salivary gland function, cholinergic agonists that act on the muscarinic receptors have the potential to increase salivary secretion. Muscarinic acetylcholine receptors are expressed in neurons of the central and peripheral nervous systems, cardiac and smooth muscle, and a variety of exocrine glands (17). Pilocarpine, a muscarinic-cholinergic agonist with mild β -adrenergic activity (7), has been found effective in the treatment of xerostomia caused by Sjögren's syndrome (18) and radiotherapy for head-and-neck cancer (19, 20). However, pilocarpine has a short duration of action (21, 22) and is associated with adverse effects, such as excessive sweating, nausea, vomiting, diarrhea, rhinitis, lacrimation, and increased urinary frequency (18–20, 23).

Cevimeline, a quinuclidine derivative of acetylcholine, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of xerostomia in patients with Sjögren's syndrome (24, 25). Preclinical studies showed that cevimeline has selective affinity for the M1 and M3 muscarinic receptors, which are the prevailing subtypes in human salivary glands (26–28), whereas M2 receptor sites predominate in cardiac tissue (29). This receptor subtype selectivity is presumed to mitigate some of the systemic adverse effects of muscarinic–cholinergic stimulation.

In randomized, controlled trials conducted to evaluate the efficacy of cevimeline in treating radiation-induced xerostomia, cevimeline-treated patients had significantly greater increases in unstimulated salivary flow than placebo recipients (30). Although the recommended dosage of cevimeline for the treatment of xerostomia in patients with Sjögren's syndrome is 30 mg t.i.d., the optimal dose for radiation-induced xerostomia may differ, because the hyposalivation associated with the latter may typically be more severe (31). In animal studies, it has been shown that cevimeline increased saliva secretion in a dose-dependent manner (27). Previous clinical studies have also demonstrated significant improvement in patients' global evaluation of dry mouth and salivary flow at study endpoint for the 30-mg group compared with the 15-mg group (24) and further increased salivary flow for the 60-mg group (25). Therefore, in the placebo-controlled studies, the dosage of cevimeline, which started at 30 mg t.i.d. for all patients, was increased to 45 mg t.i.d. after 6 weeks if adequate efficacy was not demonstrated and could be reduced to 30 mg again if the higher dosage was not tolerated. In patients with Sjögren's syndrome, a cevimeline dosage of 60 vs. 30

mg t.i.d. was associated with an increased frequency of adverse events (AEs), particularly in the gastrointestinal system, whereas there was no significant difference in the degree of symptomatic improvement experienced by patients in the two dosage groups (25). However, these were efficacy studies with short-term endpoints and a treatment duration of 6–12 weeks, which was sufficient to demonstrate the therapeutic effect of cevimeline. Thus, no data regarding the long-term safety of cevimeline treatment have been reported. This 12-month, open-label study was conducted to assess the safety of long-term use of cevimeline at a dosage of 45 mg t.i.d. in patients with radiation-induced xerostomia. The secondary objective was to assess efficacy through the patients' subjective global evaluation of mouth dryness.

METHODS AND MATERIALS

Study design

This 52-week, open-label study was conducted at 24 investigative sites in the United States. The primary objective was to evaluate the safety of cevimeline at a dosage of 45 mg t.i.d. in patients with xerostomia secondary to radiotherapy for head-and-neck cancer. The secondary objective was to assess the efficacy of cevimeline treatment on the basis of patients' subjective global evaluation of dryness of the oral cavity. This study was conducted in compliance with good clinical practice and the ethical principles of the Declaration of Helsinki. The final approved protocol and the informed consent form were reviewed by a properly constituted institutional review board.

Subject selection criteria

Subjects were required to be at least 18 years old and to have received more than 40 Gy of external beam radiotherapy for cancer in the head-and-neck region at least 4 months before entry into the study. All patients had at least one anatomically intact parotid gland and had evidence of clinically significant salivary gland dysfunction with Radiation Therapy Oncology Group Grade 2 or 3 xerostomia (32). Primary exclusion criteria included history of significant cardiovascular, gastrointestinal, or pulmonary disease; recent history of nephrolithiasis or cholelithiasis; any history of acute iritis or narrow-angle glaucoma; evidence of active liver disease, renal disease, or anemia; and active stomatitis of Grade ≥ 2 according to Common Toxicity Criteria (version 2.0) (33) for mucositis. Patients taking medications known to affect salivary function (such as anticholinergic agents and β -adrenergic antagonists) were excluded, although patients previously treated with pilocarpine (systemic or ophthalmic) were eligible to participate after a 1-day washout period. Subjects were allowed to use artificial saliva during the study period.

Treatments

Subjects who met the selection criteria underwent qualifying evaluations at the screening visit. Once screened and enrolled in the study, subjects received cevimeline 45 mg t.i.d. for the duration of the study and were seen at Week 0 (Visit 1), Week 2 (Visit 2), Week 6 (Visit 3), Week 10 (Visit 4), Week 14 (Visit 5), Week 26 (Visit 6), Week 38 (Visit 7), and Week 52 (Visit 8) during treatment. For Visits 1–4, subjects were instructed to delay one of their regularly scheduled doses on the day of the visit until arriving at the clinic or research facility.

Each subject was encouraged to complete the full course of treatment. However, a subject might discontinue study participation at any time for any reason. If a subject withdrew from the study prematurely,

the procedures scheduled for Visit 8 were performed at the time of withdrawal. The reason for early withdrawal was documented.

Study medication was dispensed in appropriately labeled bottles provided by the sponsor (Daiichi Medical Research, Montvale, NJ). Compliance with study medication was calculated from the difference between the number of capsules dispensed and the number returned.

Safety assessments

Assessment of safety was based on AEs, laboratory measures (hematology, serum chemistry, and urinalysis), vital signs, physical examinations, and 12-lead electrocardiograms. The nature of AEs, their severity, and their relationship to the study medication were assessed by each investigator throughout the study, and clinical intervention was undertaken as appropriate. A treatment-emergent AE was defined as any untoward sign, symptom, or event that occurred from the first dose of investigational medication until 30 days after the final dose, regardless of whether it was drug related. A treatment-related AE was defined as an event with a possible, probable, or definite relationship to study medication as assessed by the investigator. If data relevant to the determination of relationship to treatment were lacking, an event was deemed to be possibly treatment related. Adverse events were coded according to the World Health Organization Adverse Reaction Terminology coding dictionary (34). An AE was defined as mild (Grade 1) when it did not interfere with the subject's usual function, moderate (Grade 2) when it interfered to some extent with the subject's usual function, and severe (Grade 3) when it interfered significantly with the subject's usual function. A serious adverse event (SAE) was defined as a life-threatening event, death, inpatient hospitalization, or a persistent disability.

Efficacy assessments

The efficacy evaluation was the secondary objective in this study. The global evaluation was completed by the subject at each visit. The subject rated the level of dryness of the mouth, which was assigned a numeric score for statistical analysis: none = 0, mild = 1, moderate = 2, and severe = 3.

Sample size and statistical analysis

Sample size was based on International Conference on Harmonisation guidelines for safety studies governing the long-term use of medicines in non-life-threatening diseases. Enrollment of approximately 250 subjects was planned to ensure having 100 subjects who both completed the 52-week course and took at least 80% of the required study medication.

The evaluation of safety was based on the safety population, defined as all subjects who had taken at least 1 dose of the study medication and relayed safety information to the investigator. The evaluation of efficacy was based on the intention-to-treat population, defined as all subjects who had received at least 1 dose of the study medication. In this study, these two analysis populations were identical.

Adverse events were summarized overall, by severity, and by relationship to study medication. All SAEs were also listed and described. Demographic and baseline characteristics, vital signs, laboratory test results, and other safety data were summarized or analyzed using a paired *t* test.

The main efficacy endpoint was change in a subject's global evaluation from Visit 1 to the last visit. Each subject was classified as "improved," "no change," or "worse." If no global evaluation data were available, "no change" in xerostomia was assigned. For subjects who withdrew before the final visit (Visit 8, Week 52),

the last available post-baseline global evaluation was used for the final visit evaluation. The last observation carried forward method was used to impute missing data in the global evaluation assessment at each individual visit. Additionally, each outcome (none, mild, moderate, and severe) of the global evaluation was tabulated for each visit, and the change from baseline was analyzed with a paired *t* test and tested for a significant improvement from baseline.

RESULTS

Subject characteristics

A total of 255 subjects were enrolled in the study, all of whom took at least 1 dose of the study medication and relayed safety information to the investigator. Subject characteristics at baseline are shown in Table 1. The subjects were 76.1% male and 23.9% female, and their mean age was 58 years. The majority (88.6%) were non-Hispanic white. The median total radiation dose associated with prior radiotherapy for cancer treatment was 70 Gy (range, 36–147 Gy, including 3 subjects who had deviated from the protocol and received less than 40 Gy external beam radiotherapy before the study entry). None of the protocol deviations were considered to have impacted the efficacy or safety conclusions and were included in the analyses. The median interval between the completion of prior radiotherapy and the entry of the study was 19 months. A total of 138 subjects (54.1%) reported previous use of pilocarpine. Failure of pilocarpine treatment was reported by 100 (72.5%) of these patients, among whom the most cited reason for failure was lack of efficacy (88.0%), followed by safety (4.0%) and others (8.0%).

Disposition of subjects

A total of 192 subjects (75.3%) continued treatment for the entire 52-week study period and completed all 8 study visits. Most of the early withdrawals from the study were due to

Table 1. Baseline characteristics of the 255 subjects

Age (y)	
Mean (SD)	58.3 (11.0)
Range	21–89
Gender	
Male	194 (76.1)
Female	61 (23.9)
AJCC stage of primary head-and-neck cancer	
I	15 (5.9)
II	75 (29.4)
III	129 (50.6)
IV	4 (1.6)
Data not available	32 (12.5)
Maximum grade of mucositis experienced during radiotherapy*	
0	2 (0.8)
1	15 (5.9)
2	72 (28.2)
3	85 (33.3)
4	3 (1.2)
Data not available	78 (30.6)

Abbreviation: AJCC = American Joint Committee on Cancer. Values are number (percentage) unless otherwise noted.

* Graded according to Common Toxicity Criteria (CTC) version 2.

AEs (45 subjects). Subject or investigator request was recorded as the reason for withdrawal of 8 subjects, 3 subjects were withdrawn because of protocol violations, and 1 subject was lost to follow-up. Other reasons for termination included need for disallowed medication (2 subjects), lack of efficacy (2 subjects), and concurrent medical conditions (2 subjects).

Safety

All subjects received cevimeline 45 mg t.i.d., and the median total amount of study medication consumed per patient was 47,115 mg (range, 45–55,575 mg; mean, 38,523 mg), equivalent to approximately 349 days of treatment. Overall, 233 subjects (91.4%) experienced treatment-emergent AEs, the majority of which were mild to moderate (Table 2). The body systems most frequently affected by treatment-emergent AEs were body as a whole, in 156 subjects (61.2%), and the gastrointestinal system, in 155 subjects (60.8%). The most frequently occurring treatment-emergent AE was increased sweating, which occurred in 122 subjects (47.8%). Other frequently reported treatment-emergent AEs included nausea (14.1%), dyspepsia (13.3%), diarrhea (9.4%), constipation and tooth caries (9.0% each), rhinitis (8.6%), and vomiting (7.8%). A Grade 3 AE was reported in 52 subjects (20.4%). The most frequently reported Grade 3 AE was increased sweating (5.1%), followed by nausea (1.6%), squamous cell carcinoma, and neoplasm not otherwise specified (1.2% each).

Table 2. Summary of treatment-emergent adverse events occurring in at least 5% of the 255 subjects

Body system (preferred term)	Total*		Severe (Grade 3)	
	No.	%	No.	%
Any adverse event	233	91.4	52	20.4
Body as a whole—general disorders	156	61.2	20	7.8
Fatigue	16	6.3	1	0.4
Increased sweating	122	47.8	13	5.1
Central and peripheral nervous system disorders	42	16.5	6	2.4
Dizziness	18	7.1	0	0
Gastrointestinal disorders	155	60.8	13	5.1
Constipation	23	9.0	1	0.4
Diarrhea	24	9.4	0	0
Dyspepsia	34	13.3	1	0.4
Gastroesophageal reflux	18	7.1	1	0.4
Nausea	36	14.1	4	1.6
Tooth caries	23	9.0	0	0
Tooth disorder	19	7.5	0	0
Vomiting	20	7.8	2	0.8
Respiratory disorders	65	25.5	4	1.6
Rhinitis	22	8.6	0	0
Upper respiratory tract infection	13	5.1	0	0

* A subject reporting a preferred term more than once is counted only once for that preferred term using the most severe occurrence. A subject who reported two or more different preferred terms within the same body system is counted only once in the body system total. Subjects with adverse events in different body systems are counted only once in the overall total.

A total of 175 subjects (68.6%) experienced at least one treatment-related AE. The incidence of treatment-related AEs occurring in at least 2% of subjects is summarized in Table 3. The most frequently occurring treatment-related AE was increased sweating (121 subjects [47.5%]), followed by dyspepsia (9.4%), nausea (8.2%), diarrhea (6.3%), and dizziness (4.7%). Most of the treatment-related AEs were mild to moderate. Only 15 subjects reported severe treatment-related AEs, and in 13 of these subjects, the severe AE was increased sweating. Most treatment-related AEs (126 subjects, 49.4%) occurred within 1 week of the first dosage, and 149 subjects (58.4%) experienced at least one treatment-related AE within 1 month. The most frequently reported treatment-related AEs during the first week and first month of the study, respectively, were also increased sweating (87 subjects [34.1%] and 106 subjects [41.6%]); dyspepsia (17 subjects [6.7%] and 21 subjects [8.2%]); and nausea (15 subjects [5.9%] and 18 subjects [7.1%]).

Eighteen subjects (7.1%) experienced an SAE. The only SAE occurring in more than 1 subject was hypoesthesia, which occurred in 2 subjects. Only 1 SAE, a miscarriage, was considered by the investigator to be possibly related to study medication. All others were considered not related or unlikely to be treatment related. No subject died during the study treatment period. A total of 3 subjects died within 32 days of study completion, 2 of malignant lung neoplasms

Table 3. Summary of treatment-related* adverse events occurring in more than 2% subjects (safety population)

Body system (preferred term)	Total†		Severe (Grade 3)	
	No.	%	No.	%
Any adverse event	175	68.6	15	5.9
Body as a whole—general disorders	133	52.2	13	5.1
Fatigue	5	2	1	0.4
Hot flushes	5	2	0	0
Rigors	5	2	0	0
Increased sweating	121	47.5	13	5.1
Central and peripheral nervous system disorders	18	7.1	0	0
Dizziness	12	4.7	0	0
Gastrointestinal disorders	78	30.6	3	1.2
Constipation	10	3.9	0	0
Diarrhea	16	6.3	0	0
Dyspepsia	24	9.4	1	0.4
Gastroesophageal reflux	10	3.9	0	0
Nausea	21	8.2	2	0.8
Vomiting	10	3.9	0	0
Respiratory disorders	11	4.3	0	0
Rhinitis	9	3.5	0	0
Urinary disorders	12	4.7	0	0
Micturition frequency	10	3.9	0	0

* Possible, probable, or definite relationship to study medication.

† A subject reporting a preferred term more than once is counted only once for that preferred term using the most severe occurrence. A subject who reported two or more different preferred terms within the same body system is counted only once in the body system total. Subjects with adverse events in different body systems are counted only once in the overall total.

and the other of cardiac arrest approximately 2 weeks after the diagnosis of recurrent carcinoma of the brain.

A total of 45 subjects (17.6%) discontinued study medication because of an AE. The AE that most frequently led to discontinuation of study medication was increased sweating (15 subjects [5.9%]), followed by nausea (10 subjects [3.9%]) and vomiting (8 subjects [3.1%]). One subject reduced her dose of study medication for several days but did not discontinue treatment.

Changes from screening of some laboratory values and vital signs reached statistical significance ($p \leq 0.05$), but they were not considered to be clinically meaningful (Table 4). Seven subjects had a 12-lead electrocardiogram (ECG) result that showed a change compared with the screening ECG and was considered clinically significant. Such changes include right branch bundle block, premature ventricular complex, and non-specific T-wave abnormalities. All 12-lead ECG abnormalities that were reported as AEs were considered mild in severity except for one that was considered moderate; none was considered serious or led to discontinuation of the study medication.

Efficacy

The mean global evaluation score and change from baseline at each visit are shown in Table 5. At the final visit (Visit 8), 151 subjects (59.2%) had improvement in dry mouth, 95

(37.3%) had no change, and 9 (3.5%) had worsening compared with their evaluation at Visit 1 (baseline). The proportion of subjects with improvement from baseline in the global evaluation of dry mouth increased at each consecutive visit, from 39.2% (100 subjects) at Visit 2 to 50.6% (129 subjects) at Visit 5 and 59.2% (151 subjects) at Visit 8. The mean numeric global evaluation score improved from 2.2 at Visit 1 to 1.5 at Visit 8 (Fig. 1). The mean change from baseline in the numeric global evaluation score at each subsequent visit (Visits 2–8) is significant ($p < 0.0001$).

DISCUSSION

Overall, cevimeline 45 mg t.i.d. was well tolerated in this 52-week, open-label study in patients with radiation-induced xerostomia. Although more than 90% of patients experienced an AE, these were generally mild, and fewer than 18% of patients discontinued the medication because of an AE. No subject died during the study period, and the three deaths in the month immediately following the study period were attributed to cancer. Of the 18 reported SAEs, only 1, a miscarriage, was considered possibly related to the study drug. Cevimeline is classified in FDA Pregnancy Category C; it should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus (35).

The most frequently occurring treatment-related AE, increased sweating, reported by 47.5% of the subjects, and other frequently occurring treatment-related AEs, including dyspepsia (9.4%), nausea (8.2%), and diarrhea (6.3%), were consistent with the cholinergic agonist effect of the study medication. Most treatment-related AEs were mild to moderate and did not lead to discontinuation of treatment. Only 15 subjects (6%) reported a severe (Grade 3) treatment-related AE, and in 13 of these subjects the severe AE was increased sweating. No clinically meaningful changes in laboratory values or vital signs were seen.

The safety profile of cevimeline in the current study was comparable to that observed in two 12-week, placebo-controlled studies of cevimeline for radiation-induced xerostomia, which used a dosage of 30 mg t.i.d. that was allowed to escalate to 45 mg t.i.d. after 6 weeks (30). The most frequent treatment-emergent AE in those studies was also increased sweating, but the recorded rates of 19.0% and 18.2% were much lower than the 47.8% rate recorded in the present long-term safety study. However, the withdrawal rates of 14.6% and 13.9% recorded in the 12-week studies were comparable to the 17.6% rate of the present study (Table 6). Therefore, although increased sweating seems to be a dose-related adverse effect of cevimeline, it seemed to be tolerable for most patients and generally did not lead to discontinuation of the medication at either the 30 mg t.i.d. or the 45 mg t.i.d. dosage.

Cevimeline's tolerability has also been well documented in the treatment of Sjögren's syndrome (24, 25). In a 12-week, placebo-controlled study, treatment-related AEs were reported in 48.4% of subjects receiving 30 mg t.i.d., including increased sweating in 17.7% of subjects (24). Adverse

Table 4. Significant ($p < 0.05$) mean (SD) changes in laboratory values and vital signs recorded at various visits

Variable	Change from baseline	<i>p</i>
Laboratory values		
Hemoglobin	+0.1 g/dL at Visit 6	0.0257
Platelets	+5743–14,253/mm ³ at Visits 5, 6, 7, and 8	≤ 0.0045
RBCs	0.0–0.1 $\times 10^6/\mu\text{L}$ at Visits 7 and 8	≤ 0.0360
WBCs	+0.3–0.5 $\times 10^3/\mu\text{L}$ at Visits 5, 6, 7, and 8	≤ 0.0019
ALT	+1.85 U/L at Visits 7 and 8	≤ 0.0306
Albumin	–(0.04–0.05) at Visits 5 and 6	≤ 0.0352
AST	+1.06 U/L at Visit 8	0.0423
Total bilirubin	+0.03 mg/dL at Visit 5 and 8	≤ 0.0077
Carbon dioxide	–(1.68–2.12) at Visits 5, 6, 7, and 8	< 0.0001
Total cholesterol	+3.8 mg/dL at Visit 6	0.0282
Creatinine	+0.04 mg/dL at Visit 5	< 0.0001
Glucose	+2.91 mg/dL at Visit 8	0.0304
Urea nitrogen	–0.52 mg/dL at Visit 7	0.0452
Uric acid	–(0.10–0.18) mg/dL at Visits 6 and 7	≤ 0.0368
Vital signs		
Body weight	+3.7 (9.1) lb at Visit 8	< 0.0001
Pulse rate	+1.8–4.3 bpm at Visits 2 to 8	≤ 0.0095
Sitting SBP	–2.1 to +2.4 mm Hg at Visits 4, 6, and 7	≤ 0.0461
Sitting DBP	+1.2–2.2 mm Hg at Visits 2, 6, 7, and 8	≤ 0.0357

Abbreviations: RBC = red blood cell; WBC = white blood cell; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 5. Summary of global evaluation change and score at each visit*

Visit	Global evaluation change from baseline			Mean global evaluation score	
	Change	No. (<i>n</i> = 255)	%	Statistic (<i>n</i> = 255)	
Visit 1 (baseline)	Improved [†]			Mean (SD)	2.2 (0.7)
	No change	—	—	Median	2.0
	Worse			<i>p</i> for change	—
Visit 2	Improved	100	39.2	Mean (SD)	1.8 (0.8)
	No change	148	58.0	Median	2.0
	Worse	7	2.7	<i>p</i> for change	<0.0001 [‡]
Visit 3	Improved	114	44.7	Mean (SD)	1.7 (0.8)
	No change	133	52.2	Median	2.0
	Worse	8	3.1	<i>p</i> for change	<0.0001 [‡]
Visit 4	Improved	116	45.5	Mean (SD)	1.7 (0.8)
	No change	129	50.6	Median	2.0
	Worse	10	3.9	<i>p</i> for change	<0.0001 [‡]
Visit 5	Improve	129	50.6	Mean (SD)	1.6 (0.8)
	No change	116	45.5	Median	2.0
	Worse	10	3.9	<i>p</i> for change	<0.0001 [‡]
Visit 6	Improved	132	51.8	Mean (SD)	1.6 (0.8)
	No change	115	45.1	Median	2.0
	Worse	8	3.1	<i>p</i> for change	<0.0001 [‡]
Visit 7	Improved	136	53.3	Mean (SD)	1.6 (0.8)
	No change	108	42.4	Median	2.0
	Worse	11	4.3	<i>p</i> for change	<0.0001 [‡]
Visit 8	Improved	151	59.2	Mean (SD)	1.5 (0.8)
	No change	95	37.3	Median	1.0
	Worse	9	3.5	<i>p</i> for change	<0.0001 [‡]

* Intent-to-treat population, last observation carried forward.

[†] Improvement was defined as a change to a less severe state.

[‡] *p* value for change within each treatment group based on a paired *t* test. Statistically significant, *p* ≤ 0.05.

events were dose dependent (Table 6). In a small, short-term, placebo-controlled study, AEs were more frequently reported by patients receiving 60 mg t.i.d. than by those receiving 30 mg t.i.d. (25). The incidence of increased sweating and that of nausea were 67% and 52%, respectively, at 60 mg t.i.d. vs. 16% and 20% at 30 mg t.i.d. (25). Nausea was a more commonly reported AE in these studies of Sjögren's syndrome than in the studies of radiation-induced xerostomia and was the leading cause of discontinuation of study medicine among patients taking 60 mg t.i.d. (25). The FDA-approved

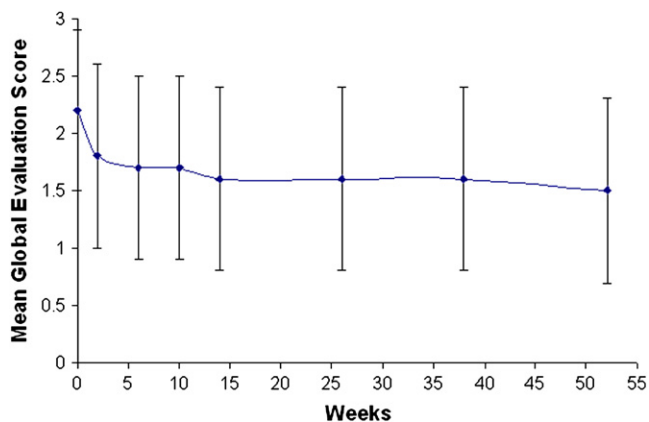


Fig. 1. Change of the mean numeric global evaluation score over the study period. Values represent mean ± SD (*n* = 255).

dosage of cevimeline for the treatment of xerostomia in patients with Sjögren's syndrome is 30 mg t.i.d.

Studies of another muscarinic agonist, pilocarpine, in the treatment of xerostomia induced by radiotherapy to the head-and-neck region found similar cholinergic side effects, which were also dose dependent (16, 17, 28). In two double-blind, placebo-controlled studies with either a fixed dosage of 5 or 10 mg t.i.d. or dose titration from 2.5 to 10 mg tid, the most common drug-related AE was increased sweating, reported by 29% of subjects taking 5 mg t.i.d. and 68% of the 10-mg group (36). Other frequently occurring treatment-related AEs included vasodilation (8% and 13% respectively), urinary frequency (9% and 12%), headache (9% and 8%), nausea (6% and 15%), and dizziness (6% and 12%) (36). In a 3-year open-label maintenance study of pilocarpine for radiation-induced xerostomia, the most common AE reported was increased sweating (55%), followed by flu-like syndrome (20%), urinary frequency (11%), and rhinitis (10%) (20). Eighteen percent of subjects withdrew because of AEs. This study allowed dosage adjustment, after an initial 5 mg t.i.d., within the range of 2.5 to 10 mg t.i.d. or b.i.d. The incidence of the most frequent AE and the proportion of patients withdrawing because of AEs are similar to those recorded in the present 12-month, open-label study of cevimeline. Important differences of the present study, however, are its shorter duration and, on the other hand, its fixed-dose design with safety as primary endpoint, which did not

Table 6. Dose-dependent adverse events of cevimeline in the treatment of xerostomia associated with radiotherapy and Sjögren's syndrome

	15 mg t.i.d.	30 mg t.i.d.		45 mg t.i.d.	60 mg t.i.d.
	SS (24)	RT* (30)	SS (24, 25)	RT	SS (25)
Duration (wk)	12	12	6–12	52	6
Discontinuation due to AE (%)	13.8	13.9–14.6	16.0–16.1	17.6	33.3
Increased sweating (%)	4.6	18.2–19.0	16–17.7	47.8	67
Nausea (%)	12.3	5.8–7.3	20–21.0	14.1	52
Dyspepsia (%)	<10	6.6	<10–16	13.3	22
Headache (%)	7.7	8.0	17.7–36	<5	30
Diarrhea (%)	13.9	4.4–7.3	12–16.1	9.4	22

Abbreviations: SS = Sjögren's syndrome; RT = radiotherapy; AE = adverse event.

* Initial dosage of 30 mg t.i.d. was allowed to escalate to 45 mg t.i.d. (40.1% and 45.3% of treatment arm) after 6 weeks if improvement in dry mouth was not demonstrated.

allow dose adjustment to achieve an optimal balance of efficacy and adverse effects.

Cevimeline has been shown to be effective in animal studies and short-term clinical trials (21, 27, 30). The present long-term study was not designed as a trial of the efficacy of cevimeline; however, efficacy assessment was the secondary objective of the study, based on the patients' global evaluation of dry mouth symptoms at each visit. The final efficacy outcomes showed that cevimeline improved dry mouth in a majority of subjects over the extended 12-month study period, and significant improvements were seen at each study visit in the mean change from baseline of the numeric global evaluation score.

Cevimeline is approved for the treatment of xerostomia associated with Sjögren's syndrome and has shown efficacy in clinical trials in patients with postirradiation xerostomia. Long-term safety data have been lacking, although xerostomia in both of these patient populations is a chronic condition

that warrants long-term treatment. The present study demonstrates the long-term safety of cevimeline in the symptomatic treatment of radiation-induced xerostomia. Moreover, the patients' global evaluations of their dry mouth symptoms showed increasing improvement over the 12-month course of the study, corroborating the finding of an earlier study of pilocarpine that the fullest possible symptomatic benefit of a sialagogic agent may not be realized until there has been time for treatment to reverse the atrophic changes in the oral mucosa caused by chronic hyposalivation (20). In addition to providing much-needed symptom relief, successful long-term treatment of xerostomia may be expected to reduce the risk for serious and debilitating oral and oropharyngeal complications. Most important, the potential benefit of treating postirradiation xerostomia should not be overlooked, because alleviation of the burdens of treatment and improvement of the quality of life are essential goals for this group of patients.

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