SYNOPSIS (Page 1 of 7)

Company: ALZA Corporation **Investigational product:** OROS® (oxybutynin chloride) **Active ingredient**: oxybutynin chloride	
Title: Open-label Safety and Dose Conversion/Determination Study of OROS® (oxybutynin chloride) for Urge Urinary Incontinence	**Trial No**.: CR005971

Investigator: Multicenter (16 centers)	**Country**: USA
No. of investigators: 16	
No. of patients: 257 (1 withdrew for personal reasons before receiving study medication)	
Trial period: Start: 18 March 1997 Last patient off treatment: 16 September 1997	
Indication: Urge urinary incontinence	

Objectives:

Primary objectives:

- To evaluate the safety of OROS® (oxybutynin chloride) in patients with urge urinary incontinence (U-UI)
- To demonstrate the persistence of effectiveness over a 12-week Maintenance Period

Secondary objectives:

- To evaluate dosing recommendations for conversion to OROS® (oxybutynin chloride) from other medications used in the treatment of U-UI
- To evaluate patient satisfaction with OROS® (oxybutynin chloride) therapy in the treatment of U-UI
- To evaluate the psychometric properties of two health-related quality-of-life instruments

STUDY PLAN

Study Design: This was a multicenter, open-label, single-treatment study. There were three study periods: Run-in, Dose Conversion/Determination, and Maintenance. During the 1-week Run-in Period, baseline incontinence, urinary frequency, and health-related quality-of-life data were collected. During the Dose Conversion/Determination Period, any previous U-UI medications were discontinued and each patient was started on OROS® (oxybutynin chloride). The dose was titrated to a clinically acceptable dose (CAD) in 5-mg increments at 7±3 day intervals to a possible maximum dose of 30 mg/day. The CAD was defined as either the minimum effective dose (ie, the dose at which the patient had no incontinent episodes for the last 2 days of the dosing interval) or the dose providing the best balance between symptomatic improvement and side effects. Patients taking IR oxybutynin at enrollment started dose titration on OROS® (oxybutynin chloride) at a dose equal to their IR oxybutynin dose; all others started at 5 mg/day OROS® (oxybutynin chloride). After the CAD was established, the patient continued for an additional week at that dose to confirm that it was appropriate. Then the patient entered the 12-week Maintenance Period that evaluated whether the U-UI reduction that was achieved by the beginning of maintenance persisted; it also further evaluated the safety of OROS® (oxybutynin chloride).

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STUDY PLAN (continued)

Main Inclusion Criteria:

- Women and men at least 18 years of age, with non-neurogenic U-UI, neurogenic U-UI, or mixed UI with a clinically significant urge component
- Currently taking medications for U-UI ("non-naive" patients) that are listed in the protocol (Section 13.1.1 of this report), including immediate-release (IR) oxybutynin chloride; ***or*** not currently taking medication for U-UI ("naive" patients)
- Naive patients must have had ≥6 U-UI episodes during the 1-week Run-in Period
- Good general health, as defined in the protocol
- Medically acceptable birth control by patients and partners throughout the study (extending 1 week after the end of study-drug treatment)
- Negative urine culture, no significant bacteria or fewer than 10 WBC/hpf on urinalysis

Treatments

Form - dosing route	OROS® (oxybutynin chloride) system - oral		
Dosing schedule	OROS® (oxybutynin chloride) 5, 10, 15, 20, 25, or 30 mg/d; Patients on 5, 15, or 25 mg/d received one, three, or five 5-mg systems per day, respectively; these were taken as a single daily dose upon arising Patients on 10, 20, or 30 mg/d received one, two, or three 10-mg systems per day, respectively; these were taken as a single daily dose upon arising		
Clinical supplies	Strength: 5 mg 10 mg	Code No.: 0004484 0004472	Control No.: 888896; MV9620003 889696; 889796
Mean duration of treatment (min-max)	105 d (1-163 d)		
Duration of trial	First patient enrolled: 18 March 1997 Last patient off treatment: 16 September 1997		
Disallowed medication	Investigational drugs within 1 month of enrollment; other medications for UI		

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STUDY PLAN (continued)

Assessments

Parameter	Screening Visit/Run-in Period	Dose-Convers. Visit[b]	Dose-Determ. Period[b]	Dose-Confirm. Visit[c]	Maint. Visit 1[d]	Maint. Visit 2[d]	Maint. Visit 3[d] or Early Termin.
Medical history	X						
Incontinence history	X						
Physical examination	X						X
PVR	X						X
Orthostatic vital signs	X						X
Adverse events	X	X	X	X	X	X	X
ECG	X						X
Laboratory tests	X						X
Urinalysis	X						X
Pregnancy test	X						X
U-IIQ	X[a]				X		X
U-UDI	X[a]				X		X
PSOR	X				X		X
PUD	Completed during Run-in Week (week following Screening Visit) and during Maintenance Weeks 1, 4, 8, and 12						
P-ACEA	To be completed by physician if severe or intolerable anticholinergic effects occur						

Abbreviations: CAD=clinically acceptable dose; convers=conversion; determ=determination; confirm=confirmation; maint=maintenance; termin=termination; PVR=post-void residual; U-IIQ=Urge-Incontinence Impact Questionnaire; U-UDI=Urge-Urogenital Distress Inventory; P-ACEA=Physician's Anticholinergic Effects Assessment; PSOR=Patient Satisfaction and Overall Rating; PUD=Patient Urinary Diary

a Administered at beginning and end of Run-in Week

b Only non-naive patients went through dose-conversion-visit assessments. All patients went through the dose-determination portion of the study, during which dose was titrated to the CAD.

c Visit at end of the dose-confirmation portion of the study (ie, beginning of Maintenance Period).

d Maintenance Visit 1 was at the end of Maintenance Week 4, Maintenance Visit 2 was at the end of Maintenance Week 8, and Maintenance Visit 3 was termination (at the end of Maintenance Week 12).

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STATISTICAL METHODS

Ninety-five percent confidence intervals were constructed for 1) mean reduction in number of U-UI episodes/week from Baseline (Run-in Period) to Week 1 of Maintenance; and 2) mean change in number of U-UI episodes/week from Week 1 of Maintenance to end of study. Primary efficacy analysis was construction of the two 95% confidence intervals. In addition, a paired t-test was used to analyze change from Baseline to each visit in the Maintenance Period in efficacy data.

BASELINE CHARACTERISTICS & PATIENT DISPOSITION

	Naive Patients[a]	Non-naive Patients [a,b]	All Patients
No. patients enrolled (M/F)	185 (12/173)	72 (10/62)	257 (22/235)
No. patients enrolled/Race:			
• Caucasian	169	67	236
• Black	7	4	11
• Asian	1	1	2
• Hispanic	7	0	7
• Other	1	0	1
No. patients enrolled/Type of UI			
• Neurogenic	2	10	12
• Other than neurogenic	183	62	245
Mean age (min-max) (y)	58.7 (18-92)	62.0 (34-98)	59.6 (18-98)
Incontinence history:			
• Incontinent ≤1 y	16	6	22
• Incontinent >1 y	169	66	235
Reason for patient withdrawal:			
• Adverse event	14 (7.6%)	6 (8.5%)	20 (7.8%)
• Death	1 (0.5%)	0	1 (0.4%)
• Lack of efficacy	2 (1.1%)	2 (2.8%)	4 (1.6%)
• Protocol violation	2 (1.1%)	2 (2.8%)	4 (1.6%)
• Noncompliance	3 (1.6%)	1 (1.4%)	4 (1.2%)
• Personal reason	7 (3.8%)	2 (2.8%)[b]	9 (3.5%)
• Lost to follow-up	2 (1.1%)	0	2 (0.8%)
• Other	3 (1.6%)[c]	0	3 (1.2%)

a Naive patients were those not taking U-UI medication during the Run-in Period at the beginning of the study; non-naive patients were those taking such medications during the Run-in Period

b One of these non-naive patients did not receive study drug and terminated prematurely.

c Includes one patient who did not meet entry criteria and two who had an insufficient number of U-UI episodes.

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EFFICACY RESULTS

A total of 219 patients were included in the efficacy analysis; 38 were excluded (31 who discontinued prematurely and had no urinary diary data during the Maintenance Period; 6 who completed the study but did not have Maintenance Week 1 urinary diary data; 1 who did not receive study medication). A clinically meaningful reduction from Baseline to Maintenance Week 1 was demonstrated in the mean number of weekly U-UI episodes (18.8 to 3.9), the mean number of weekly total UI episodes (22.2 to 5.2), and the mean weekly void frequency (81.1 to 69.1). This level of effectiveness was sustained through the 12-week Maintenance Period: The mean number of weekly U-UI episodes was 3.9 at Maintenance Week 1 and 2.8 at Endpoint; the mean number of weekly total UI episodes was 5.2 at Maintenance Week 1 and 4.0 at Endpoint; and the mean weekly void frequency was 69.1 at Maintenance Week 1 and 66.8 at Endpoint. Patients achieved effectiveness across all doses of OROS® (oxybutynin chloride) (5 through 30 mg/day), supporting dose titration to effect.

The subset of the patients who converted from other U-UI medications to OROS® (oxybutynin chloride) (ie, “non-naive” patients) achieved substantial, additional reductions from Baseline to Maintenance Week 1 in U-UI (13.3 to 2.5) and total UI (15.1 to 3.8), and their mean weekly total void frequency was reduced from 72.9 to 66.7. Again this level of effectiveness was sustained through the 12-week Maintenance Period for U-UI (2.5 episodes at Maintenance Week 1 to 2.6 at Endpoint), total UI (3.8 to 4.0), and void frequency (66.7 to 67.3). The proportion of these patients who were totally continent more than doubled from Baseline to Endpoint (21.7% to 51.7%). Importantly, the same effect was seen among patients who were taking IR oxybutynin formulations at enrollment (18.9% continent at Baseline to 48.6% at Endpoint).

Patients reported improvement in health-related quality of life after treatment with OROS® (oxybutynin chloride): They reported that symptoms were less bothersome, as assessed by the Urge-Urogenital Distress Inventory (U-UDI), and they reported improvement in all eight domains assessed by the Urge-Incontinence Impact Questionnaire (U-IIQ) (ie, “activities,” “travel,” “physical activities,” “feelings,” “relationships,” “sexual functioning,” “night bladder control,” and “satisfaction with treatment”). Consistent with these quality-of-life findings, 92.9% of patients expressed satisfaction with OROS® (oxybutynin chloride) at the end of the study, as assessed by the Patient Satisfaction and Overall Rating (PSOR) questionnaire.

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SAFETY RESULTS

Analysis of safety data from the 256 patients who received study medication demonstrated that OROS® (oxybutynin chloride) was well tolerated at doses up to 30 mg/day for up to 23 weeks treatment duration. Twenty (7.8%) patients discontinued because of adverse events (AEs) and one (0.4%) died of causes unrelated to treatment. Nausea was the AE most commonly causing discontinuation (2.3% of patients). No patient previously using medication for the treatment of U-UI discontinued within the first week of dose conversion, supporting the safety of the dose-conversion and dose-determination recommendations for these patients. Of the 49 patients treated with doses >20 mg/day, three (3.8%) discontinued because of an AE: one at 25 mg/day (for anticholinergic effects) and two at 30 mg/day (one for anticholinergic effects; one for cerebral ischemia and pneumonia considered unrelated to treatment).

Eighteen patients experienced serious AEs during the study; in 15 of these patients, the events were considered unrelated to treatment. One patient died due to a myocardial infarction and congestive heart failure; the investigator judged these events to be unrelated to study drug. Two patients with gastroesophageal reflux had serious AEs considered possibly related to study treatment (exacerbations of gastroesophageal reflux, one patient at a dose of 10 mg/day and one at 30 mg/day).

At least one AE was reported by 86.3% of patients. The most frequently reported AE was dry mouth (in 58.6% of patients). Moderate or severe dry mouth was reported by 23.0% of patients, but only 1.6% of patients discontinued study medication prematurely because of dry mouth.

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CONCLUSIONS

The efficacy and safety results lead to the following conclusions:

- Clinical effectiveness of OROS® (oxybutynin chloride) was achieved by Maintenance Week 1 and sustained through the 12-week Maintenance Period, with pronounced reduction or elimination of U-UI and total UI episodes, and reduction of the total void frequency.
- Patients achieved reduction or elimination of U-UI and UI across all doses studied, supporting dose titration to effect.
- Patients who converted from other medications—including IR oxybutynin— achieved substantial, additional reductions in U-UI and total UI, as well as reductions in total void frequency.
- OROS® (oxybutynin chloride) was well tolerated at doses from 5 through 30 mg/day for treatment durations of up to 23 weeks.
- A clinically efficacious dose was defined for 91.3% of patients included in the efficacy analysis, confirming that the dose-conversion and dose-determination recommendations are appropriate.
- Patients had a low rate of discontinuation from study because of AEs, with 7.8% prematurely discontinuing study medication for AEs and 1.6% discontinued for dry mouth.
- As with IR oxybutynin formulations, physicians should exercise caution in prescribing OROS® (oxybutynin chloride) for patients who have gastroesophageal reflux and/or who are concurrently taking drugs that can cause or exacerbate esophagitis.
- Almost all patients reported satisfaction with OROS® (oxybutynin chloride) therapy, as well as improvements in health-related quality of life, at the end of study.

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