

TRIAL IDENTIFICATION AND PROTOCOL SUMMARY	
Company: ALZA CORPORATION	
Investigational products: OROS [®] (oxybutynin chloride) and D-TRANS [™] oxybutynin *	
Active ingredient: Oxybutynin chloride or oxybutynin base	
Title: Efficacy and Safety of OROS [®] (oxybutynin chloride) and D-TRANS [™] oxybutynin in Middle-aged and Elderly Women with Urinary Incontinence	Trial No.: CR005965

Investigator: Multicenter	Country: USA
Trial period: Start: December 2, 1995 End: December 2, 1996	No. of investigators: 9 No. of patients: 134
Indication: Urge urinary incontinence (U-UI)	

OBJECTIVES
<p>Primary objective: To compare the efficacy of controlled-release OROS[®] (oxybutynin chloride) with oral placebo in middle-aged and elderly patients with U-UI, and to evaluate the side-effect profiles of OROS[®] (oxybutynin chloride) and oral placebo</p> <p>Secondary objectives:</p> <ul style="list-style-type: none"> • To compare the efficacy and safety of OROS[®] (oxybutynin chloride) and an immediate-release active control, IR oxybutynin, in this patient population • To determine steady-state plasma and urine concentrations of oxybutynin and its active metabolite, desethyloxybutynin <p>Other objectives:</p> <ul style="list-style-type: none"> • To evaluate the anticholinergic side-effect profile of OROS[®] (oxybutynin chloride) and IR oxybutynin, the use of incontinence pads, patient assessments of treatments, effect of treatments on cystometrogram (CMG) measurements, and void volumes • To compare the efficacy and the anticholinergic effects of D-TRANS[™] oxybutynin to D-TRANS[™] placebo (See Appendix 13.)

STUDY PLAN
Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, active-controlled, parallel-group study with a 1-week, single-blinded placebo run-in period.

*D-TRANS[™], the trademarked name for ALZA's transdermal therapeutic system, was known as TTS (Transdermal Therapeutic System) at the time the protocol for this study was written.

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Title: Efficacy and Safety of OROS[®] (oxybutynin chloride) and D-TRANS[™] oxybutynin in Middle-aged and Elderly Women with Urinary Incontinence**Trial No.:** CR005965**STUDY PLAN (continued)****Main inclusion criteria:**

- Women, 40 years of age or older, with average number of U-UI episodes of ≥ 7 voids/day at baseline, average urinary frequency of 10 voids/day, and CMG-demonstrated detrusor contraction and/or severe "must void" urge at bladder filling volume ≤ 400 mL
- Women with mixed urinary incontinence (UI), provided that symptoms and/or signs of stress incontinence are not the predominant manifestation of UI, and U-UI episodes associated with urgency can be differentiated from urge incontinence episodes not associated with urgency
- Creatinine clearance greater than 50 mL/min
- Normotensive, with or without hypertensive medication; no postural hypotension
- No medications used for U-UI; not refractory to medications used to treat U-UI

Treatments

Test Products	Code Numbers	Control Numbers	Doses and Modes of Administration
OROS [®] (oxybutynin chloride), 5 mg	0000584	790894	Single daily dose of one, two, or three tablets = 5, 10, or 15 mg/day
IR oxybutynin chloride capsules, 1.7 mg	AZ50071 02-1	95H012	One or two 1.7-mg capsules q8h = 5 or 10 mg/day
IR oxybutynin chloride capsules, 2.5 mg	AZ50071 01-1	95H011	Two 2.5-mg capsules q8h = 15 mg/day
OROS [®] placebo Lot 1	0000588	785694	One or two capsules q8h
OROS [®] placebo Lot 2	0000588	802995	One or two capsules q8h
IR placebo capsules	AZ50071 03-1	95J013	One or two capsules q8h
D-TRANS [™] placebo	0001075	803995	One or two D-TRANS [™] placebo systems worn for 3.5 days
D-TRANS [™] oxybutynin base, 7.5 mg/day	0000606	791694	One or two D-TRANS [™] oxybutynin systems worn for 3.5 days

Duration of Treatment: Six weeks, after 1-week, single-blind, placebo run-in period

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STUDY PLAN (continued)	
Assessments	
Efficacy:	<p>The primary efficacy outcome measurement is the change in the number of U-UI episodes per week from baseline to end of treatment, as recorded in the Patient Urinary Diary (PUD).</p> <p>Additional efficacy outcome measurements are as follows:</p> <ul style="list-style-type: none"> • Total number of incontinence episodes (from PUD) • Total void frequencies per week (from PUD) • Number of incontinence pads changed each day because of wetness (from PUD) • Maximum void volume in 24 hours and 24-hour void volume • Void volume plus postvoid residual volume (PVR) • Cystometric measurements • Patient satisfaction and overall rating regarding impact of treatment • Subjective assessment of urinary symptom severity
Pharmacokinetics:	<p>Plasma samples were analyzed for enantiomers of oxybutynin and desethyloxybutynin; relationship between dose and trough drug concentrations was established; urine concentrations of drug and metabolite in 24-hour collections were measured.</p>
Safety:	<p>The following safety measurements were made:</p> <ul style="list-style-type: none"> • Adverse events • Anticholinergic side effects • Vital signs after dosing • PVR volume • Topical effects of D-TRANS[™] • Laboratory tests

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STATISTICAL METHODS
<p>The primary hypothesis tested in this study was that the treatment difference between the OROS[®] (oxybutynin chloride) group and the oral placebo group in the mean change in the number of U-UI episodes per week from baseline to end of study was equal to zero.</p> <p>A two-way analysis of variance (ANOVA) and a two-way analysis of covariance (ANCOVA) that included the three randomized oral treatment groups (OROS[®] [oxybutynin chloride], IR oxybutynin, and oral placebo) were used for the primary efficacy analysis.</p> <p>The ANOVA/ANCOVA method was also used for the analysis of several other continuous efficacy parameters and variables. The Cochran-Mantel-Haenszel (CMH) tests were used for the analysis of categorical measurements. A CMH test for general association was applied to the dichotomous data, and a CMH test for row mean score difference was applied to the ordinal categorical data. The Fisher's Exact test was used for the analysis of categorical demographic variables, selected baseline variables, and anticholinergic adverse events. The two-sample t-test was used for the analysis of continuous demographic and baseline variables. The pairwise nonparametric van Elteren tests were performed with center and baseline weekly U-UI episodes category (4 categories: 1 = less than 11, 2 = 11-20, 3 = 21-30, 4 = more than 30) as stratification factors.</p> <p>In addition to the statistical tests applied for the analysis of selected parameters and variables, sample means of efficacy and safety data were summarized by treatment group without performing formal statistical tests.</p> <p>Separate analyses were applied to the oral and D-TRANS[™] treatment groups, and the results of the transdermal treatments are presented in Appendix 13.</p>

BASELINE CHARACTERISTICS & PATIENT DISPOSITION
Patient Population: <ul style="list-style-type: none"> • Planned: 120 • Total enrolled: 134 (82 in oral treatment groups, 52 in D-TRANS[™] groups) • Sex: Female • Mean age: 58.7 years, range 40 to 85 years

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EFFICACY RESULTS					
Primary Efficacy Results	OROS [®] Oxybutynin (n=34)	IR Oxybutynin (n=32)	Oral Placebo (n=16)	OROS [®] vs Oral Placebo p-value	Overall Comparison p-value
Adjusted mean (SEM) change from baseline:					
<ul style="list-style-type: none"> No. of U-UI episodes/week Proportion of patients who had no U-UI episodes/week 	-18.6 (1.5) 64.7%	-15.6 (1.6) 34.4%	-10.2 (2.0) 18.8%	0.001 0.001	0.005 0.006
Secondary Efficacy Results	OROS [®] Oxybutynin (n=34)	IR Oxybutynin (n=32)	Oral Placebo (n=16)	OROS [®] vs Oral Placebo p-value	Overall Comparison p-value
Adjusted mean (SEM) change from baseline:					
<ul style="list-style-type: none"> Total incontinence episodes/week Total void frequency/week Number of incontinence pads used/week 	-20.0 (1.5) -20.5 (2.7) -12.4 (1.2)	-16.8 (1.7) -17.5 (2.9) -10.3 (1.3)	-11.1 (2.1) -11.2 (4.1) -4.8 (1.6)	<0.001 0.062 <0.001	0.003 0.006 0.002
Proportion of patients who achieved total continence	50.0%	28.1%	12.5%	0.003	0.012
<p>OROS[®] (oxybutynin chloride) was significantly (p=0.001) more effective than placebo and was not different (p=0.181) from IR oxybutynin in reducing U-UI episodes. At the end of treatment, significantly more patients in the OROS[®] (oxybutynin chloride) group than in the placebo group had no U-UI episodes (p=0.001), and 50% of patients in the OROS[®] (oxybutynin chloride) group were continent, compared with 12.5% of patients in the placebo treatment group (p=0.003). At the end of treatment, patients in the OROS[®] (oxybutynin chloride) group used significantly fewer incontinence pads per week than did patients in the oral placebo group (p=0.001).</p>					

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PHARMACOKINETIC RESULTS

The mean R- and S-oxybutynin and R- and S-desethyloxybutynin predose (trough) plasma concentrations increased linearly with each dose in both OROS[®] (oxybutynin chloride) and IR oxybutynin treated patients, suggesting that the pharmacokinetics of OROS[®] (oxybutynin chloride) and IR oxybutynin do not change with increasing doses up to 15 mg. The predose (trough) and postdose concentrations of oxybutynin and desethyloxybutynin with OROS[®] (oxybutynin chloride) controlled-release administration were similar. For IR oxybutynin, postdose drug concentrations were higher than predose (trough) concentrations, reflecting the immediate dissolution and rapid absorption of drug within an hour after IR oxybutynin administration.

A lower drug-to-metabolite ratio for IR oxybutynin treatment as compared with OROS[®] (oxybutynin chloride) treatment was observed, indicating that oxybutynin is metabolized to a lesser extent when administered from OROS[®] (oxybutynin chloride). Negligible amounts of the drug were excreted in the urine after either OROS[®] or IR treatment. The dose-response modeling showed a trend toward higher efficacy with OROS[®] (oxybutynin chloride) and a reduced probability of dry mouth as compared with IR oxybutynin at the same dose.

SAFETY RESULTS

Safety Measurements	OROS [®] Oxybutynin (n=34)	IR Oxybutynin (n=32)	Oral Placebo (n=16)
Number (%) of patients discontinued study medication prematurely because of AE	0	2 (6.3%)	1 (6.3%)
Number (%) of patients reporting any AE	34 (100%)	32 (100%)	12 (75.0%)
Number (%) of patients reporting any anticholinergic AE	31 (91.2%)	32 (100%)	11 (68.8%)
Number (%) of patients reporting dry mouth	29 (85.3%)	32 (100%)	8 (50.0%)

No serious AEs were reported in this study. All oral study medications were well tolerated, and the overall AE profiles of OROS[®] (oxybutynin chloride) and IR oxybutynin appeared to be similar.

No patients in the OROS[®] (oxybutynin chloride) group discontinued study medication prematurely because of AEs. Two patients in the IR oxybutynin group and one patient in the placebo group discontinued study medication secondary to AEs. The most frequently reported anticholinergic AE was dry mouth, with each active treatment group reporting significantly more dry mouth than did the oral placebo group (OROS[®] [oxybutynin chloride]: p=0.014; IR oxybutynin: p=0.001). However, fewer patients treated with OROS[®] (oxybutynin chloride) reported dry mouth than did patients treated with IR oxybutynin (85.3% vs 100%, p=0.054). In the D-TRANS[™] oxybutynin treatment group, more than half the patients reported adverse events, and application site reactions were the major cause of early discontinuation from D-TRANS[™] oxybutynin.

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CONCLUSIONS
<ul style="list-style-type: none">• OROS[®] (oxybutynin chloride) is significantly more effective than oral placebo in reducing the number of U-UI episodes and in producing full continence.• OROS[®] (oxybutynin chloride) and IR oxybutynin have similar efficacy in the treatment of U-UI.• Dose-response modeling of the data shows a slightly wider therapeutic index for OROS[®] (oxybutynin chloride) than for IR oxybutynin.• OROS[®] (oxybutynin chloride) was well tolerated, with a lower incidence of dry mouth and the expected profile for other anticholinergic side effects.

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Study C-95 031 D-TRANS™ Oxybutynin Administration for Urge Urinary Incontinence

Study Design and Plan Description

Study C-95-031 was a multicenter, randomized, double-blind, placebo-controlled, parallel treatment study with a run-in week of single-blind placebo followed by randomization of patients to 1 of 5 treatment groups.

The study was conducted in 134 middle-aged and elderly women (ages 40 to 85 years) with urge urinary incontinence (U-UI). Enrolled patients were given the two oral placebos (OROS® and immediate-release [IR]) and a transdermal (D-TRANS™) placebo during the first single-blind week.

After randomization, the study was essentially conducted as two trials:

1. A double-blind, placebo- and active-controlled comparison of OROS® (oxybutynin chloride), IR oxybutynin, and oral placebo in 82 patients
2. A double-blind, placebo-controlled evaluation of a D-TRANS™ oxybutynin formulation and D-TRANS™ placebo in 52 patients

Although patient populations for each trial (oral formulations or D-TRANS™ formulation) were enrolled from the same sites using one central randomization schedule, the treatment schedules and doses used were different. This summary focuses on the methods, results, and conclusions of the D-TRANS™ oxybutynin formulation trial.

Treatments

Treatments were applied to patients randomized in the D-TRANS™ oxybutynin active treatment group in the following sequence:

1. One active D-TRANS™ oxybutynin system every 3.5 days for 2 weeks
2. One active and one placebo system every 3.5 days for 2 weeks
3. Two D-TRANS™ oxybutynin systems every 3.5 days for 2 weeks

Efficacy Measurements

Patient Urinary Diary: The primary efficacy outcome measured was the change in the number of U-UI episodes per week from baseline to end of study as recorded in the Patient Urinary Diary.

Cystometric Assessment: At screening (Visit 2, Day 0) and at end of study (Visit 9, Day 49), the following measurements were recorded for each 100 mL increase in bladder filling volume: urge to void score (0-2), detrusor contraction (none, tonic, or phasic), and bladder pressure.

Patient Satisfaction and Overall Rating (PSOR): At the end of the placebo run-in period and at the end of each 2-week treatment interval (Days 7, 21, 35, and 49), patients completed a PSOR general questionnaire on the impact of treatment.

Subjective Assessment of Urinary Symptom Severity (SAUSS): Using a 5-point scale (0-4), patients recorded on the SAUSS the timing and severity of their symptoms of daytime frequency, nocturia, incontinence, and urgency after each week of treatment (Days, 7, 14, 21, 28, 35, 42, and 49).

Safety Measurements

Adverse events (AEs), vital signs, and laboratory measurements were used to assess safety in this study.

Brief Summary of Adverse Events

Two patients who were later randomized to the OROS[®] (oxybutynin chloride) group experienced application site reactions from D-TRANS[™] placebo during the run-in period that continued through the study start.

At least one AE was reported by 94.3% (33/35) of patients in the D-TRANS[™] oxybutynin group and by 76.5% (13/17) of patients in the D-TRANS[™] placebo group. In the D-TRANS[™] oxybutynin group, 57.1% (20/35) patients reported skin adverse events, primarily application site reactions, whereas only 17.6% (3/17) patients in the D-TRANS[™] placebo group reported similar AEs. Application site reactions such as rash or irritation were coded as application site reaction-

other. All the skin adverse events were considered related to study treatment in both treatment groups. All of those occurring in the D-TRANS™ placebo group were rated as mild in severity; those in the D-TRANS™ oxybutynin treatment group were predominantly moderate or severe in severity.

At least one anticholinergic AE was reported by 85.7% (30/35) of patients in the D-TRANS™ oxybutynin group and 70.6% (12/17) of patients in the D-TRANS™ placebo group. The most frequently reported anticholinergic AEs in the D-TRANS™ oxybutynin and placebo groups were dry mouth (65.7% and 35.3%, respectively), nausea (34.3% and 11.8%, respectively), somnolence (31.4% and 41.2%, respectively), constipation (28.6% and 35.3%, respectively), and blurred vision (20.0% and 47.1%, respectively).

Deaths, Other Significant Adverse Events

No deaths or significant adverse events were reported by either D-TRANS™ treatment group in this study.

Laboratory Values Over Time

No clinically significant pattern or trend was observed in mean changes in laboratory parameters (CBC, electrolytes, LFT, creatinine clearance, and UA) from baseline to end of study within either the D-TRANS™ oxybutynin or the D-TRANS™ placebo group, or between groups.

Individual Clinically Significant Abnormalities

There were no clinically significant laboratory abnormalities during the study for patients treated with either of the D-TRANS™ treatments.

Vital Signs

No clinically significant changes were observed in the mean values for heart rate (HR) and blood pressure (BP) in patients in the D-TRANS™ oxybutynin or D-TRANS™ placebo group. No clinically significant differences were observed between the D-TRANS™ treatment groups in mean value changes for HR and BP or in orthostatic vital signs.

Electrocardiogram

No statistically significant differences were observed within or between the D-TRANS™ treatment groups in PR, QRS, or QT intervals from baseline to end of study. Five (15.6%) patients treated with D-TRANS™ oxybutynin developed new ECG findings at the end of study. None were considered clinically significant. None of the patients treated with D-TRANS™ placebo developed new ECG findings at the end of study.

Safety Conclusions

In the D-TRANS™ oxybutynin group, more than half the patients reported adverse events of the skin system. Application site reactions were the major cause of early discontinuation from D-TRANS™ oxybutynin.

Discussion and Overall Conclusions

This study evaluated the feasibility of a transdermal oxybutynin dosage formulation (D-TRANS™ oxybutynin) for the treatment of U-UI. In a pairwise comparison, D-TRANS™ oxybutynin did not have a significantly greater treatment effect (reduction in number of U-UI episodes) than D-TRANS™ placebo. This may be attributed to the number of patients who discontinued treatment early because of application site reactions, and/or may indicate that the dose delivered was not in a therapeutic range. Application site reactions were the major cause of early discontinuation from the D-TRANS™ oxybutynin treatment group, indicating that this formulation is not acceptable for further study.