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TRIAL IDENTIFICATION AND PROTOCOL SUMMARY	
Company: ALZA Corporation **Investigational product**: OROS® (oxybutynin chloride) **Active ingredient**: oxybutynin chloride	
Title: The Maximum Tolerated Dose and Minimum Effective Dose of OROS® oxybutynin Compared to Ditropan® in the Treatment of Patients with Urge or Mixed Urinary Incontinence (UI)	**Trial No.**: CR005968

Investigator: Multicenter	**Country**: USA
Trial period: Start: 30 July 1996 End: 26 February 1997	**No. of investigators**: 14 **No. of patients**: 105
Indication: Urge urinary incontinence (U-UI)	

Objectives:

First objective in the protocol was as follows:

- Compare the efficacy of OROS® (oxybutynin chloride) to immediate-release (IR) oxybutynin (Ditropan®) at the final dose level.

Additional objectives were as follows:

- Demonstrate the therapeutic equivalence of OROS® (oxybutynin chloride) and IR oxybutynin.
- Determine the minimum effective dose (MED) and/or maximum tolerated dose (MTD) of OROS® (oxybutynin chloride) compared with IR oxybutynin for the treatment of urge or mixed UI.
- Evaluate the safety profile of OROS® (oxybutynin chloride) (at doses up to 30 mg per day) compared with IR oxybutynin (at doses up to 20 mg per day, the maximum recommended daily dose of IR oxybutynin).
- Determine the plasma concentrations of oxybutynin and desethyloxybutynin at the MED, MTD, or maximum allowable dose (MAD).

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STUDY PLAN

Study Design: This was a randomized, multicenter, double-blind, parallel-group, dose-titration study designed to compare the efficacy and safety of OROS® (oxybutynin chloride) and IR oxybutynin at the MED, MTD, or maximum allowed dose (MAD). The planned enrollment was approximately 100 patients with U-UI or mixed UI provided that stress UI was not the predominant manifestation of mixed UI.

Main Inclusion Criteria:

- Men and women, age 40 to 75, with urge or mixed UI provided that stress UI was not the predominant manifestation of mixed UI.
- Patients who were currently taking immediate-release oxybutynin (Ditropan®), hyoscyamine (Levsin® Cystospaz®), or propantheline (Pro-Banthine®), or who had taken Ditropan® in the past for urge or mixed UI. Patients who had taken and discontinued Ditropan® for urge or mixed UI should not have discontinued due to failure of efficacy.
- Patients who had at least six urge UI episodes per week recorded on the Run-in Diary after washout of anticholinergic medications.
- Patients who were able to differentiate incontinent episodes associated with urgency from incontinent episodes not associated with urgency when recording incontinent episodes in the diary. The Run-in Diary after washout of all anticholinergic medications must have demonstrated that the number of urge incontinent episodes per week was greater than the number of incontinent episodes not associated with urgency per week.

Treatments

Form - dosing route	Matching gelatin capsules - oral	
Medication	OROS® (oxybutynin chloride) 5 mg systems ALZA Corporation	Ditropan® (oxybutynin chloride) 5 mg tablets Hoechst Marion Roussel
Batch No.	Code No. 0002824 Control No. 838796	Lot No. K37336

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STUDY PLAN (continued)	
Treatments (continued)	
Dosage	OROS® (oxybutynin chloride): 5,10,15, 20, 25, 30 mg/d IR oxybutynin (Ditropan®): 5,10,15, 20 mg/d Patients in both treatment groups began study-drug treatment at an oxybutynin dose of 5 mg/d. The dose was changed in 5 mg increments at 4- to 7-day intervals, depending on the safety and efficacy of the current dose. The MAD for IR oxybutynin was 20 mg/d, which is the maximum daily adult dose specified in its labeling. Because controlled delivery of oxybutynin by an OROS® dosage form could potentially reduce side effects, it was believed that the drug could possibly be tolerated at doses higher than 20 mg/d. Consequently, the MAD for OROS® (oxybutynin chloride) was 30 mg/d administered as a single daily dose.
Duration of treatment	OROS® (oxybutynin chloride): 11-70 days IR oxybutynin: 10-61 days
Duration of trial	30 July 1996 to 26 February 1997
Disallowed medication	• Other drugs considered effective in the treatment of U-UI, including hyoscyamine (Levsin®, Cystospaz®), propantheline (Pro-Banthine®), dicyclomine (Bentyl®), flavoxate (Urispas®), imipramine (Tofranil®), phenylpropanolamine, pseudoephedrine (Sudafed®), baclofen (Lioresal®), or hyoscyamine/atropine (Urised®). • Drugs (including over-the-counter medications) with anticholinergic or anticholinergic-like effects. • Investigational drugs (except for oxybutynin) within a period of 1 month or five times the half-life of the investigational drug before study enrollment (whichever was longer).

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STUDY PLAN (continued)

Assessments

Parameter	Schedule				
	Screening Visit	Treatment Visit 1	Treatment Visit ≥2	Maint. Visit 1	Maint. Visit 2
Physical exam & history	X				
Voided volume & post-void residual (PVR)	X				X
Clinical laboratory tests	X				X
Urinalysis	X				X
Urine drug screen	X				X
Pregnancy test	X				X
ECG	X				X
Orthostatic vital signs	X	X	X	X	X
Anticholinergic Effects Assessment (ACEA) questionnaire		X	X	X	X
Adverse events		X	X	X	X
Sample for plasma drug and metabolite concentration analysis				at 0, 1, 2, 4 hours after 1st AM dose	at 0 hours
Subjective Assessment of Urinary Symptom Severity (SAUSS) questionnaire					X
Patient Satisfaction and Overall Rating (PSOR) questionnaire					X
Patient Urinary Diary	During IR oxybutynin Run-in Period (only for patients on IR oxybutynin [Ditropan®] before enrollment) During Off-medication Run-in Period During Maintenance Period				

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STATISTICAL METHODS
A two-way analysis of covariance (ANCOVA) was used for analysis of the primary efficacy parameter, as prospectively specified. The analysis of variance (ANOVA)/ANCOVA method was used for the analysis of several other continuous efficacy parameters. 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 and selected baseline variables and anticholinergic adverse events. The two-sample t-test was used for the analysis of continuous demographic and baseline variables. In addition to the statistical tests applied for the analysis of selected parameters and variables, efficacy and safety data were summarized by treatment group without performing formal statistical tests.

BASELINE CHARACTERISTICS & PATIENT DISPOSITION		
	OROS® (oxybutynin chloride)	IR oxybutynin
No. patients entered (F/M)	50/3	47/5
Mean age (min-max) (y)	59.2 (34-75)	59.6 (34-76)
Reason for patient withdrawal[a]: Protocol deviation Personal reason Adverse event[b]	 1 1 5	 0 1 5

a. Includes all patients who discontinued study medication early
b. One serious adverse event (SAE) occurred in the IR oxybutynin group: a patient developed a subdural hematoma of unknown relationship to study drug that resolved with treatment; no SAEs occurred in OROS® group.

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EFFICACY RESULTS

Overview: OROS® (oxybutynin chloride) and IR oxybutynin achieved comparable reductions in number of U-UI episodes per week: adjusted mean reductions were 20.7 and 21.6 U-UI episodes per week, respectively. Elimination of U-UI episodes was achieved by 52.2% of patients receiving OROS® (oxybutynin chloride) treatment and 51.1% of patients receiving IR oxybutynin treatment. Patients achieved efficacy (ie, no U-UI episodes) across all dose levels studied for both treatments. Several additional efficacy measurements (total UI, void volume, and PVR) also supported the efficacy of OROS® (oxybutynin chloride).

Efficacy Measurements Change from Baseline (Adjusted mean [SEM])	OROS® (oxybutynin chloride)	IR oxybutynin	95% CI of difference (OROS® versus IR oxybutynin)	p-value
Weekly U-UI	-20.7 (1.3)	-21.6 (1.3)	-2.8, 4.6	0.636
Total UI	-22.1 (1.5)	-23.3 (1.6)	-3.1, 5.6	0.567
Total Void Frequency (normal and incontinent)	-2.9 (2.0)	-14.4 (2.1)	5.7, 17.2	<0.001

PHARMACOKINETIC RESULTS

Following OROS® (oxybutynin chloride) treatment, plasma concentrations were relatively constant over time, although they increased with dose. Following IR oxybutynin administration, plasma concentrations of all four analytes (R-oxybutynin, S-oxybutynin, R-desethyloxybutynin, and S-desethyloxybutynin) increased at 1 hour and decreased thereafter. These results are consistent with the findings of a previous study in healthy volunteers (C-94-010-04 1995). The plasma concentrations at each dose level were measured following the first 5 mg dose of IR oxybutynin administered in the morning. Peak plasma concentrations were similar at all dose levels.

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SAFETY RESULTS

Both OROS® (oxybutynin chloride) and IR oxybutynin were well tolerated, and, with the exception of dry mouth, had comparable safety profiles. Significantly fewer patients reported dry mouth with OROS® (oxybutynin chloride) at up to 30 mg/d than with IR oxybutynin at up to 20 mg/d (67.9% versus 86.5%, p=0.035). Also, significantly fewer patients reported moderate or severe dry mouth with OROS® (oxybutynin chloride) (24.5% versus 46.1%, p=0.025). The dose-response modeling results demonstrated that an increase in IR oxybutynin dose results in more reports of dry mouth than a comparable increase in OROS® (oxybutynin chloride) dose—a finding that supports the findings of the dry mouth safety analysis.

No discernible pattern or trend in AEs resulted in study discontinuation with either treatment, and there were no deaths in the study. There was one serious AE in the IR oxybutynin group that was of unknown relationship to study drug and resolved with treatment.

CONCLUSIONS

The results of this study lead to the following conclusions:

- OROS® (oxybutynin chloride) and IR oxybutynin were comparably efficacious in reducing the number of U-UI episodes and producing full continence.
- Patients achieved efficacy (no U-UI) across all doses studied for OROS® (oxybutynin chloride) and IR oxybutynin, supporting individual dose titration to efficacy.
- Patients taking once-a-day OROS® (oxybutynin chloride) achieved efficacy comparable to that of patients taking IR oxybutynin up to three to four times daily.
- OROS® (oxybutynin chloride) and IR oxybutynin were both well tolerated, and with the exception of dry mouth, they had comparable overall safety profiles.
- Significantly fewer patients reported dry mouth, or moderate/severe dry mouth, with OROS® (oxybutynin chloride) than with IR oxybutynin.

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