

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-897**

**CHEMISTRY REVIEW(S)**

DEC 16 1998

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-897    **CHEM.REVIEW #:** 3    **REVIEW DATE:** 16-DEC-1998

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
Original	17-DEC-1997	19-DEC-1997	31-DEC-1997
Amendment	07-DEC-1998	08-DEC-1998	08-DEC-1998
Amendment	11-DEC-1998	11-DEC-1998	11-DEC-1998

**NAME & ADDRESS OF APPLICANT:**

Alza Corp.  
1010 Joaquin Road  
P.O. Box 7210  
Mountain View, CA 94039-7210

**DRUG PRODUCT NAME**

Proprietary:	Ditropan XL
Nonproprietary/USAN:	Oxybutynin chloride extended release tablets
Code Name/#:	3011050
Chem.Type/Ther.Class:	3S

**PHARMACOL.CATEGORY/INDICATION:** Anticholinergic/Treatment of urge urinary incontinence, urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia.

**DOSAGE FORM:**

Modified release tablets

**STRENGTHS:**

5, 10 mg

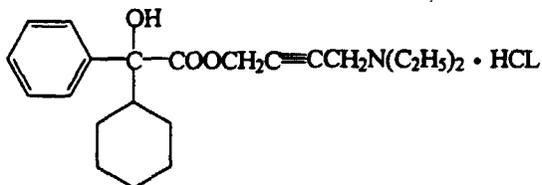
**ROUTE OF ADMINISTRATION:**

oral

**DISPENSED:**

Rx    OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**



- benzeneacetic acid, a-cyclohexyl-a-hydroxy-,4-(diethylamino)-2-butynyl ester hydrochloride
- 4-(diethylamino)-2-butynyl a-phenylcyclohexanecarboxylate hydrochloride

Molecular formula: C<sub>22</sub>H<sub>32</sub>ClO<sub>3</sub>

Molecular weight: 393.9

CAS # 1508-65-2

**SUPPORTING DOCUMENTS:**

See Chemistry Reviews # 1 and #2.

**RELATED DOCUMENTS:**

none

**PATENT STATUS:**

See Chemistry Review #1.

**CONSULTS:**

See Chemistry Reviews #1 and #2.

**REMARKS/COMMENTS:**

The December 7, 1998 amendment is the response to the December 7, 1998 Information Request letter.

The December 11, 1998 amendment is a revision of the 12/7/98 amendment.

**CONCLUSIONS & RECOMMENDATIONS:**

The sponsor has satisfactorily addressed all the CMC issues. This NDA may be approved. The sponsor should be informed that future printings of the blister pack holders and blister card labels may need to be revised.

cc:

Orig. NDA 20-897

HFD-580/Division File

HFD-580/Chemist/MJRhee/DLin

HFD-580/CSO/Olmstead

R/D Init by: MJ Rhee

filename: nda20897.3 (doc)

*MJRhee 12/16/98*

*-151*

*12/16/98*

\_\_\_\_\_  
David T. Lin, Ph.D.  
Review Chemist

Olmstead

DEC - 7 1998

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-897    **CHEM.REVIEW #:** 2    **REVIEW DATE:** 06-DEC-1998

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	17-DEC-1997	19-DEC-1997	31-DEC-1997
Amendment	06-AUG-1998	10-AUG-1998	13-AUG-1998
Amendment	30-OCT-1998	02-NOV-1998	05-NOV-1998
Amendment	16-NOV-1998	17-NOV-1998	21-NOV-1998
Amendment	20-NOV-1998	23-NOV-1998	23-NOV-1998

**NAME & ADDRESS OF APPLICANT:**

Alza Corp.  
1010 Joaquin Road  
P.O. Box 7210  
Mountain View, CA 94039-7210

**DRUG PRODUCT NAME**

Proprietary:	Ditropan XL
Nonproprietary/USAN:	Oxybutynin chloride extended release tablets
Code Name/#:	3011050
Chem.Type/Ther.Class:	3S

**PHARMACOL.CATEGORY/INDICATION:** Anticholinergic/Treatment of urge urinary incontinence, urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia.

**DOSAGE FORM:**

Modified release tablets

**STRENGTHS:**

5, 10 mg

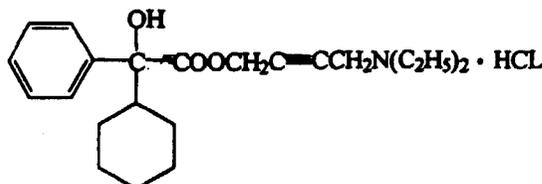
**ROUTE OF ADMINISTRATION:**

oral

**DISPENSED:**

X Rx       OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**



- benzeneacetic acid, a-cyclohexyl-a-hydroxy-4-(diethylamino)-2-butynyl ester hydrochloride
- 4-(diethylamino)-2-butynyl a-phenylcyclohexaneglycolate hydrochloride

Molecular formula: C<sub>22</sub>H<sub>32</sub>ClO<sub>3</sub>  
Molecular weight: 393.9  
CAS # 1508-65-2

**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND				N/A	N/A
IND				N/A	N/A
NDA 17-577	Ditropan	Alza Corp.	Approved	7/16/75	N/A
DMF				9/22/97	12/19/96
DMF				10/21/98	10/22/97
DMF				10/21/98	1/20/98
DMF				10/21/98	10/27/97
DMF				1/6/95	7/2/96
DMF				10/21/98	7/30/97
DMF					6/9/97
DMF				8/18/97	11/6/97
DMF				9/3/98	11/6/97
DMF					11/6/97
DMF				6/23/93	11/6/97

\*The yellow tablet coating replaces the green coating (4/30/98 amendment).

**RELATED DOCUMENTS:**

none

**PATENT STATUS:**

See Chemistry Review #1.

**CONSULTS:**

1. The Division of Biopharmaceutics has been consulted for the cumulative drug release specifications.
2. The EER was sent to Compliance on February 4, 1998. It was returned as acceptable on July 7, 1998 (see Chemistry Review #1).
3. The proposed tradename, Ditropan XL, was sent to the Nomenclature and Labeling Committee on October 15, 1997. The Committee determined the tradename to be acceptable (see Chemistry Review #1).

**REMARKS/COMMENTS:**

The August 6, 1998 amendment includes updated stability data.

The October 30, 1998 amendment includes revised blister pack holder labels.

The November 16, 1998 amendment includes revised container labels and package insert.

The November 20, 1998 amendment is the response to the November 10, 1998 Information Request letter.

**CONCLUSIONS & RECOMMENDATIONS:**

This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter.

cc:

Orig. NDA 20-897

HFD-580/Division File

HFD-580/Chemist/MJRhee/DLin

HFD-580/CSO/Olmstead

R/D Init by: MJ Rhee

filename: nda20897.2 (doc)

*MJRhee* 12/7/98

*/S/*

2/6/98

David T. Lin, Ph.D.  
Review Chemist



**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND				N/A	N/A
IND				N/A	N/A
NDA 17-577	Ditropan	Alza Corp.	Approved	7/16/75	N/A
DMF				9/22/97	12/19/96
DMF				10/21/98	10/22/97
DMF				10/21/98	1/20/98
DMF				10/21/98	10/27/97
DMF				1/6/95	7/2/96
DMF				10/21/98	7/30/97
DMF					6/9/97
DMF				8/18/97	11/6/97
DMF				9/3/98	11/6/97
DMF					11/6/97
DMF				6/23/93	11/6/97

\*The yellow tablet coating replaces the green coating (4/30/98 amendment).

**RELATED DOCUMENTS:**

none

**PATENT STATUS:**

Patent No.	Type	Expiration	Patent Owner
5,674,895	Formulation	5/22/2015	Alza Corp.
5,082,668	Formulation	9/16/2003	Alza Corp.
4,783,337	Formulation and Method of Use	9/16/2003	Alza Corp.
4,612,008	Formulation	9/16/2007	Alza Corp.
4,519,801	Formulation	5/28/2002	Alza Corp.
4,327,725	Formulation	5/4/1999	Alza Corp.

**CONSULTS:**

1. The Division of Biopharmaceutics has been consulted for the cumulative drug release specifications.
2. The EER was sent to Compliance on February 4, 1998. It was returned as acceptable on July 7, 1998
3. The proposed tradename, Ditropan XL, was sent to the Nomenclature and Labeling Committee on October 15, 1997. The Committee determined the tradename to be acceptable (Feb. 18, 1998 ).

**REMARKS/COMMENTS:**

Oxybutynin chloride is an anticholinergic agent used in the treatment of urge urinary incontinence, urgency and frequency arising from overactivity of the bladder's detrusor muscle. It has been marketed in the United States for more than 20 years as an immediate release tablet (Ditropan® tablets, Hoechst Marion-Roussel, NDA 17-577). Ditropan® is now currently being manufactured and distributed by Alza Corporation. For this NDA, Alza has developed a once-daily controlled release tablet for the oral administration of oxybutynin chloride; also referred to as OROS®. There are two dosage strengths, 5 and 10 mg, which are designed to deliver 5 and 10 mg of oxybutynin chloride over 24 hours, respectively. The 5 and 10 mg tablets release oxybutynin chloride at a nominal rate of 0.3 and 0.6 mg/h, respectively. Alza's controlled release oral osmotic technology is currently being utilized in a variety of approved drug products, including Procardia XL (nifedipine) Extended Release Tablets (Pfizer, NDA 19-684; Division of Cardio-Renal Drug Products), and Glucotrol XL (glipizide) Extended Release Tablets (Pfizer, NDA 20-329; Division of Metabolism and Endocrine Drug Products).

The April 30, 1998 amendment includes the following: 1) a change in the overcoat color from green to yellow, 2) a change in ownership of the drug substance supplier, 3) a revised product assay method, and 4) a corrected method validation report.

The August 6 and September 30, 1998 amendments include updated stability data.

The June 30, 1998 amendment include revised labeling of the container labels.

**CONCLUSIONS & RECOMMENDATIONS:**

This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter.

cc:

Orig. NDA 20-897

HFD-580/Division File

HFD-580/Chemist/MJRhee/DLin

HFD-580/CSO/Olmstead

R/D Init by: MJ Rhee

filename: nda20897.1 (doc)

*MJRhee 10/28/98*

*^ /S/*

*10/28/98*

\_\_\_\_\_  
David T. Lin, Ph.D.  
Review Chemist

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 20-897**

**PHARMACOLOGY REVIEW(S)**

ORIGINAL

OCT 21 1998

**Review and Evaluation of Pharmacology/Toxicology Data**

HFD-580/Alex Jordan, PhD

NDA 20-897

Sponsor: Alza Corporation

Submission: December 17, 1997

Ditropan XL (oxybutynin chloride) Extended Release Tablets

**Table of Contents**

Pharmacology	2
Toxicology	4
Overall Summary	6
Recommendations	6

NDA 20-897  
HFD-580  
AJordan

ISI  
Alex Jordan, PhD

10/21/98

Previous IND:

Ditropan XL (OROS; oxybutynin chloride) is indicated for the treatment of urge urinary incontinence, urgency, and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia.

Oxybutynin chloride is currently marketed in the United States for symptomatic relief of urge urinary incontinence as Ditropan tablets or syrup and as generic oxybutynin chloride products. Oxybutynin exists in two enantiomeric forms, with most of the anticholinergic properties residing in the (R)-isomer. The marketed immediate release oxybutynin chloride products (Ditropan and various generics), and Ditropan XL are racemates.

In addition to safety information provided by 20 years of clinical experience with the marketed products, the nonclinical toxicology data for oxybutynin chloride in mice, rats, hamsters, guinea pigs, rabbits, and dogs show that oxybutynin has a low overall toxicity profile. Most of the drug's adverse side effects are related to its anticholinergic pharmacological activity. Pharmacology and toxicology studies were reviewed in IND

Animal studies reported in the literature and submitted in regulatory filings indicate that oxybutynin is rapidly absorbed, metabolized, and excreted after oral administration. Due to the short half-life of oxybutynin, the currently marketed immediate-release formulations of oxybutynin chloride require multiple daily dosing; the recommended dose is 5 mg administered orally two to four times per day.

Ditropan XL extends delivery of oxybutynin chloride, providing for once-a-day dosing. According to the sponsor, the OROS oral osmotic technology has been well characterized and currently is used in eight US marketed products. The OROS system uses osmotic energy to deliver oxybutynin chloride at a controlled rate for up to 24 hours after dosing. This OROS system comprises a nonerodible, semipermeable membrane enclosing an osmotically active bilayer core. The bilayer core is composed of a drug layer containing oxybutynin chloride and excipients and an osmotic engine ("push layer") containing osmotic agents and polymers. An orifice is drilled through the membrane on the drug layer side of the tablet. In the aqueous environment of the gastrointestinal (GI) tract, water is absorbed through the membrane at a rate determined by the properties of the membrane and osmolality of the core constituents. This water causes the osmotic layer to expand, pushing the drug layer through the orifice. Drug delivery is essentially zero-order as long as the osmotic gradient remains constant. The depleted system does not dissolve and is excreted in the feces.

The following US marketed products use the OROS oral osmotic system technology:

ACUTRIM (phenylpropanolamine)  
COVERA-HS (verapamil hydrochloride)  
DYNACIRC CR (isradipine)  
EFIDAC 24 Chlorpheniramine (chlorpheniramine maleate)  
EFIDAC 24 Pseudoephedrine (pseudoephedrine hydrochloride)  
GLUCOTROL XL (glipizide)  
PROCARDIA XL (nifedipine)  
VOLMAX (albuterol sulfate)

The nonclinical safety of Ditropan XL was demonstrated in two studies: 1) a 30-day oral toxicity study in dogs, which demonstrated no treatment-related gastrointestinal irritation or other significant signs of systemic toxicity, and 2) an established rabbit colon model, which demonstrated only mild irritation to the rabbit colon after 6 hours of continuous delivery of oxybutynin chloride to a single site. The proposed daily dosing recommendations for Ditropan XL are 5 to 30 mg daily (approximately 0.07-0.43 mg/kg qd for a 70 kg patient). The rabbit colon toxicology study was previously reviewed under IND

#### Pharmacology (sponsors summary)

Oxybutynin is a tertiary amine ester with anticholinergic (antimuscarinic), spasmolytic (muscle relaxant), and local anesthetic properties. The anticholinergic effects together with the spasmolytic activity are responsible for the relaxant effects of the drug on the detrusor muscle of the urinary bladder, reducing undesirable spontaneous contractions, increasing the bladder (vesical) capacity and delaying the initial desire to void. Oxybutynin thus decreases the urgency and frequency of both incontinent episodes and voluntary urination in patients suffering from urinary incontinence.

The anticholinergic activity of oxybutynin is considered the primary mechanism of action in the treatment of urinary incontinence. In vitro studies have shown that the drug competitively antagonizes detrusor contractions induced by muscarinic agents or electrical stimulation of parasympathetic pathways. Several studies have investigated the selectivity of oxybutynin for muscarinic receptors at different tissue sites, but the true number and characteristics of muscarinic receptor subclasses at which oxybutynin binds have not been completely established. Oxybutynin is also a smooth muscle relaxant of the urinary bladder, gastrointestinal system, and uterus. In contrast to the anticholinergic activity of oxybutynin, which resides predominantly in the R-isomer, its spasmolytic actions are not stereoselective and are 500 times weaker. The contribution of the drug's local anesthetic properties to its effects on detrusor activity has not been determined.

Urinary incontinence results from abnormalities in the normal function of the lower urinary tract that acts both to store and to expel urine by bladder filling and bladder emptying. The coordinated actions of the detrusor muscle, the internal sphincter and the external sphincter are responsible for bladder filling and emptying. Bladder filling requires detrusor relaxation, closed sphincters and the absence of involuntary bladder contractions. Bladder emptying requires coordinated detrusor contraction, concomitant relaxation of the internal and external sphincters and the absence of anatomic obstruction. Anatomic, neurologic and pharmacologic conditions that interfere with these functions can result in urinary incontinence.

There are four major categories of incontinence: urge incontinence, stress incontinence, mixed (urge and stress) incontinence and overflow incontinence. Treatments vary as to the patient's type of incontinence and its severity. Ditropan XL has been developed as a once-daily controlled release oral oxybutynin formulation for the treatment of urge urinary incontinence, urgency, and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia. Urge incontinence is usually associated with the urodynamic findings of involuntary detrusor contractions. When a neurologic disorder is present, the involuntary detrusor activity is referred to as detrusor hyperreflexia.

## Toxicology

In subchronic and chronic multiple dose studies, relatively low oral doses resulted in mydriasis and morphologic changes in the parotid gland in rats (2-20 mg/kg/d for 2 to 24 months; 7-70 times the approved human daily dose), and mydriasis and xerostomia in dogs (2 mg/kg/d for 2 months). After oral doses of 60 to 200 mg/kg/d for 3 to 24 months in rats, effects included increased salivation, hyperactivity, decreased body weight gains, hypersensitivity to stimulation, ataxia, pulmonary congestion, edema, hemorrhage, and hemothorax, pathologic changes in the liver and kidney, and increased mortality. No evidence of carcinogenicity was reported from a 2-year study in rats at 400 times (on a mg/kg basis) the human dosage. After oral doses of 4 to 16 mg/kg/d for 2 to 12 months to dogs, tachycardia, hyperactivity, hyperventilation, ataxia, and increased liver, kidney, and ovarian weights have been reported.

Studies performed with mice, hamsters, and rabbits demonstrated no serious adverse reproductive effects or teratogenic potential of oxybutynin; in rats, no adverse reproductive or teratogenic effects were observed at doses up to 20 mg/kg. In rats, at doses (>50 mg/kg) associated with maternal toxicity (eg, decreased maternal body weight gains or facial staining), increased gestation periods, pup mortality, and fetal abnormalities (ventricular septal defects and supplementary ribs), decreased post partum weight gain in pups, and slight delays in pinna unfolding, in startle response, and eye opening have been reported in rats.

Oxybutynin tested negative for mutagenic activity in assays with *Salmonella typhimurium*, *Escherichia coli*, *Schizosaccharomyces pomphoiciformis*, and *Saccharomyces cerevisiae*. The genotox studies in bacteria are from published studies, the studies in yeast are from the PDR and no data are available.

The delivery-specific toxicity of Ditropan XL was investigated in a 30-day oral toxicity study in dogs. This study examined local gastrointestinal effects and monitored systemic effects of Ditropan in beagle dogs administered OROS systems for 30 consecutive days. Two strengths of Ditropan XL, 10 mg (one of the proposed strengths for marketing) and immediate-release Ditropan 5 mg tablets were evaluated in this study.

### Rabbit Colon Model Study

The delivery-specific toxicity of Ditropan XL was investigated in an established rabbit colon model study. This study examined the local effects of oxybutynin, as delivered from OROS 5 mg systems, on the colonic mucosa of rabbits. The results of the study in the rabbit colon model indicate that OROS (oxybutynin chloride) is a mild local irritant.

### Published Nonclinical Metabolism of Oxybutynin Chloride

Results from animal studies support clinical reports of rapid absorption after oral administration of oxybutynin chloride from immediate-release formulations. Peak blood levels in rats, rabbits, and dogs are generally within 1 to 2 hours after oral administration. Oxybutynin is rapidly metabolized in rat liver microsomes to N-desethyloxybutynin and oxybutynin N-oxide. The primary metabolite in rat plasma is phenylcyclohexylglycolic acid. Primary metabolic pathways are de-ethylation, ester hydrolysis, oxygenation of the cyclohexyl ring, and conjugation. In

addition to phenylcyclohexylglycolic acid and its glycine conjugate, at least six other minor metabolites have been identified, including an active metabolite, N-desethyloxybutynin (~5% in the urine). Excretion is primarily through the feces in rats. In dogs, excretion was approximately equal in urine and feces after either oral or intravenous administration.

In humans, Ditropan XL results in a lower C<sub>max</sub> of oxybutynin and slightly higher AUC than Ditropan tablets (Table 1).

**Thirty day repeated dose oral toxicity study of Oros (oxybutynin chloride) administered via capsule to dogs** Alza report TR-96A601-059.

Four male and four female beagle dogs per group were given 4 empty Oros systems, 4 x 10 mg oxybutynin systems (40 mg Oros), 3 x 15 mg oxybutynin systems (45 mg Oros) or 8 x 5 oxybutynin tables (40 mg Ditropan). Dogs were dosed daily for 30 days.

**Clinical signs:** Greater frequency of dilated pupils and incidence of dry nose, dry mouth and decreased defecation were seen in Ditropan treated dogs compared to controls or Oros treated dogs. There was increased frequency of anticholinergic activity in the high dose Oros dogs compared to low dose and controls.

**Body weight and feed consumption:** No significant changes.

**Ophthalmology:** No effects.

**Hematology:** No treatment related effects.

**Clinical chemistry:** No treatment related effects.

**Urinalysis:** No treatment related effects.

**Organ weights:** There was a statistically significant decrease in absolute and relative (to brain and body wt) thymus weight in Ditropan treated dogs compared to controls. No other changes were noted.

**Gross pathology:** No effects seen including the GI tract.

**Histopathology:** Exam was limited to oral pharynx, larynx, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon (3 levels) and gross lesions. There were no gross lesions. There were no microscopic lesions in the GI tract that suggested a treatment related effect for any group.

**Pharmacokinetics:** Blood samples were drawn weekly during the study. On day 29, extensive sampling was done for pK data. 24 hr sampling showed the Ditropan tablet treated dogs had a mean C<sub>max</sub> of 25.6 ng/ml and a T<sub>max</sub> of approximately 1 hr. The mean C<sub>max</sub> for the 40 and 45 mg/d OROS treated dogs were 3.3 and 3.6 ng/ml respectively with a T<sub>max</sub> of approximately 6 hrs. The sponsor did not provide AUC data but it looks like the Ditropan tablet treated dogs received a much greater exposure to oxybutynin than the OROS treated dogs.

**Conclusion:** Oxybutynin is an approved drug and the OROS system of drug delivery results in a lower C<sub>max</sub> and a slightly higher AUC with more constant drug exposure. The only animal study not previously reviewed was the 1 month dog study that was requested by the Division to examine the effects of several OROS systems on the intestinal mucosa. Treated dogs received either 3 or 4 systems daily for 30 days without appreciable intestinal toxicity. There was a teratogenic effect of oxybutynin (ventricular septal defects) in rats at a dose that produced maternal toxicity. The dose was 50 mg/kg or approximately 18 times the exposure in humans taking the maximum dose. Since Ditropan XL produces a lower C<sub>max</sub> and only slightly higher AUC, I don't feel it is necessary to change the pregnancy category from B to C.

**Recommendation:** Pharmacology recommends approval of Ditropan XL (oxybutynin chloride) for urge urinary incontinence.

**Labeling:** Under Carcinogenesis, Mutagenesis, Impairment of Fertility: The first sentence should be changed to

This labeling change should also be made for Ditropan and all generics.

*Label is satisfactory*

*ISI*  
*12/16/98*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 20-897**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION

**NDA#:** 20-897

DEC 16 1998

**SPONSOR:** ALZA Corporation

**DRUG:** OROS or Ditropan XL (oxybutynin chloride)

**DRUG CLASS:** 1S

**INDICATION:** For the treatment of urge urinary incontinence, urgency, frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia.

**DOCUMENTS REVIEWED:** Original submission: Dec. 17, 1997.  
Amendments: Aug. 6, 1998; Sept. 30, 1998; Nov. 16, 1998.  
Sponsor FAX: Dec. 4, 1998.

**DATES:** Date received by Medical Division, HFD-580: December 22, 1997  
Date received by Division of Biometrics, HFD-715: June 18, 1998  
User Fee Date: December 19, 1998

**MEDICAL REVIEWER:** Daniel Shames, M.D., HFD-580

**STATISTICAL REVIEWER:** Sonia Castillo, Ph.D., HFD-715

### Major Review Issues:

- The regulatory requirement for independent trials is questionable; some of the same subjects and study investigators participated in more than one trial. This is particularly a problem for Studies C-95-049 and C-97-020.
- The design for assessing dry mouth was not adequate in Study C-97-020.
- Study C-95-049 did not demonstrate equivalence between OROS and Ditropan on the endpoint of the difference in the change from baseline in the number of weekly urge urinary incontinence episodes using the *a priori* definition for equivalence.
- Sponsor's input data used for efficacy analysis differed from the input data used by the statistical reviewer.
- Length of time that the patient was on their maintenance dose of test agent for the chronic condition of urge urinary incontinence was short (no more than two weeks).
- Efficacy subgroup analyses for age, gender, and race were not presented for two of the three trials.
- Intent-to-treat analyses were not presented in the study reports.

### Summary of Phase 3 Controlled Trials

The following table gives an overview of the three studies for the indication sought.

Study No.	No. of Centers	Design	Test Agent and Oral Daily Dose (mg)	Type of Control	Sample Size Enrolled: Completed	Study Pop. (Sex, Condition, Age)
C-95-031	9	MC,R,DB, PG,FDE	OROS 5, 10, 15 IR oxybutynin 5, 10, 15 Placebo none	P, A	34:32 32:30 16:15 Total - 82:77	Female with U-UI or mixed UI in which U-UI predominated. (Mean age=58.7 y; Range=41-85 y)
C-95-049	13	MC,R,DB, PG,DT	OROS 5, 10, 15, 20, 25, 30 Ditropan 5, 10, 15, 20	A	53:46 52:46 Total - 105:92	Female (n=97) and male (n=8) patients with U-UI or mixed UI in which U-UI predominated. (Mean age=59.4 y; Range=34-76 y)
C-97-020	19	MC, R, DB, A, PG	OROS 5, 10, 15, 20, 25, 30 Ditropan 5, 10, 15, 20	A	111:104 115:105 Total - 226:209	Female (n=202) and male (n=24) patients with U-UI or mixed UI in which U-UI predominated. (Mean age=59.2 y; Range=40-76 y)

\* MC: Multicenter; R: Randomized; DB: double-blind; P: Placebo; A: Active; PG: parallel group; FDE: fixed dose escalation; U-UI: urge urinary incontinence; UI: urinary incontinence; DT: dose titration to effect, tolerance, or maximum dose

\* A: Active, Pl: Placebo

The submission included three controlled safety and efficacy and one uncontrolled safety and efficacy study. This statistical review will focus on the three controlled studies. These three studies are as follow:

**C-95-031:** Efficacy and Safety of OROS (oxybutynin chloride) and TTS oxybutynin in Middle-aged and Elderly Women with Urinary Incontinence.

**C-95-049:** The Maximum Tolerated Dose with Minimum Effective Dose OROS (oxybutynin chloride) Compared with Immediate-release (Ditropan) oxybutynin in the Treatment of Patients with Urge or Mixed Urinary Incontinence.

**C-97-020:** Comparison of Dry Mouth During Treatment with OROS (oxybutynin chloride) and Ditropan in Patients with Urge Urinary Incontinence.

This review will present an overview of each study, describe the study conduct, safety and efficacy data collected, the sponsor's primary efficacy analyses and results, this reviewer's evaluation of the study and sponsor's analyses, and this reviewer's alternate primary efficacy analyses and conclusions. The Medical Reviewer is Daniel Shames.

INTRODUCTION AND PROPOSED INDICATION.....6

**PART I - Study C-95-031: Efficacy and Safety of OROS (oxybutynin chloride) and TTS oxybutynin in Middle-aged and Elderly Women with Urinary Incontinence.**

<u>Section</u>	<u>Page</u>
1.0 INTRODUCTORY BACKGROUND.....	7
2.0 OBJECTIVES OVERVIEW.....	7
3.0 STUDY DESIGN AND PROCEDURES.....	7
3.1 Screening Period.....	7
3.2 Placebo Run-In Period.....	8
3.3 Treatment Period.....	8
4.0 STUDY VARIABLES.....	9
4.1 Safety Variables.....	9
4.2 Primary Efficacy Endpoint.....	9
4.3 Secondary Efficacy Endpoints.....	9
5.0 SPONSOR'S STATISTICAL ANALYSIS METHODS.....	10
5.1 Analysis Groups and Pooling of Investigators.....	10
5.2 Definition of Baseline and Endpoint Measurements.....	10
5.3 Analysis Methods of the Primary Efficacy Endpoint.....	10
6.0 STUDY HYPOTHESIS AND SAMPLE SIZE.....	11
7.0 OTHER STUDY INFORMATION.....	11
7.1 Principal Investigators.....	11
7.2 Patient Enrollment and Randomization.....	12
7.3 Patient Accountability and Evaluability.....	12
8.0 SPONSOR'S RESULTS.....	13
8.1 Primary Efficacy Results.....	13
8.2 Safety Results.....	14
9.0 REVIEWER'S COMMENTS ON STUDY DESIGN AND ANALYSES.....	14
10.0 STATISTICAL REVIEWER'S ANALYSES AND RESULTS.....	14
11.0 REVIEWER'S RECOMMENDATION.....	15

**PART II - Study C-95-049: 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).**

<u>Section</u>	<u>Page</u>
1.0 INTRODUCTORY BACKGROUND.....	16
2.0 OBJECTIVES OVERVIEW.....	16

3.0 STUDY DESIGN AND PROCEDURES.....	16
3.1 Therapeutic Responder Screening Trial.....	16
3.2 Study Screening Procedure.....	17
3.3 Run-In Period.....	18
3.4 Treatment Period.....	18
3.5 Maintenance Period.....	18
4.0 STUDY VARIABLES.....	19
4.1 Safety Variables.....	19
4.2 Primary Efficacy Endpoint.....	19
4.3 Secondary Efficacy Endpoints.....	19
5.0 SPONSOR'S STATISTICAL ANALYSIS METHODS.....	19
5.1 Analysis Groups and Pooling of Investigators.....	19
5.2 Definition of Baseline and Endpoint Measurements.....	19
5.3 Analysis Methods of the Primary Efficacy Endpoint.....	20
6.0 STUDY HYPOTHESIS AND SAMPLE SIZE.....	20
7.0 OTHER STUDY INFORMATION.....	20
7.1 Principal Investigators.....	20
7.2 Patient Enrollment and Randomization.....	21
7.3 Patient Accountability and Evaluability.....	22
8.0 SPONSOR'S RESULTS.....	22
8.1 Primary Efficacy Results.....	22
8.2 Safety Results.....	23
9.0 REVIEWER'S COMMENTS ON STUDY DESIGN AND ANALYSES.....	23
10.0 STATISTICAL REVIEWER'S ANALYSES AND RESULTS.....	24
11.0 REVIEWER'S RECOMMENDATION.....	25

**PART III - Study C-97-020: Comparison of Dry Mouth during Treatment with OROS (oxybutynin chloride) and Ditropan in Patients with Urge Urinary Incontinence.**

<u>Section</u>	<u>Page</u>
1.0 INTRODUCTORY BACKGROUND.....	26
2.0 OBJECTIVES OVERVIEW.....	26
3.0 STUDY DESIGN AND PROCEDURES.....	26
3.1 Therapeutic Responder Screening Trial.....	26
3.2 Study Screening Procedure.....	27
3.3 Run-In Period.....	28
3.4 Dose Titration Period.....	28
3.5 Maintenance Period.....	28
4.0 STUDY VARIABLES.....	29

4.1 Safety Variables.....29

4.2 Primary Endpoint.....29

4.3 Secondary Endpoints.....29

**5.0 SPONSOR’S STATISTICAL ANALYSIS METHODS.....29**

    5.1 Analysis Groups and Pooling of Investigators.....29

    5.2 Definition of Baseline and Endpoint Measurements.....30

5.3 Analysis Methods of the Primary Endpoint.....30

    5.3.1 Per Protocol Analyses.....30

    5.3.2 Post-Hoc Analyses.....30

5.4 Analysis Methods of the Efficacy Parameters.....30

    5.4.1 Per Protocol Analyses.....30

    5.4.2 Post Hoc Analyses.....31

**6.0 STUDY HYPOTHESIS AND SAMPLE SIZE.....31**

**7.0 OTHER STUDY INFORMATION.....32**

7.1 Principal Investigators.....32

    7.2 Patient Enrollment and Randomization.....32

7.3 Patient Accountability and Evaluability.....33

**8.0 SPONSOR’S RESULTS.....34**

8.1 Efficacy Results.....34

8.2 Dry Mouth Results.....35

8.3 Safety Results.....36

**9.0 REVIEWER’S COMMENTS ON STUDY DESIGN AND ANALYSES.....36**

**10.0 STATISTICAL REVIEWER’S ANALYSES AND RESULTS.....40**

    10.1 Efficacy Results.....40

**11.0 REVIEWER’S RECOMMENDATION.....41**

**CONCLUSIONS.....42**

**SIGNATURE PAGE.....43**

**APPENDIX I.....44**

## **INTRODUCTION AND PROPOSED INDICATION**

Urge urinary incontinence (U-UI), a common type of urinary incontinence (UI), is characterized by the involuntary loss of urine associated with a strong desire to void (urgency). Stress incontinence is characterized by involuntary loss of urine during coughing, sneezing, laughing, or during physical activities that increase intra-abdominal pressure. Urinary incontinence is most prevalent among the elderly and affects more women than men. U-UI is the second most common type of UI in women.

Oxybutynin is the gold standard for the treatment of patients with U-UI, urgency, and frequency arising from overactivity of the bladder's detrusor muscle. Oxybutynin has been marketed in the United States for more than 20 years as an immediate release (IR) formulation (Ditropan or IR oxybutynin) and is recognized as a safe and effective treatment for the symptoms of U-UI. OROS is a different formulation of Ditropan that delivers oxybutynin chloride at a controlled rate. Dry mouth, the most frequently reported side effect, is often cited as the major reason that patients discontinue therapy.

The sponsor has proposed the following indication for OROS.

With the three clinical trials submitted in this application, the sponsor has sought to demonstrate the following three objectives: 1) that OROS was superior to placebo in the treatment of U-UI; 2) that OROS was therapeutically equivalent to Ditropan in the treatment of U-UI; and 3) that use of OROS for the treatment of U-UI resulted in less patients experiencing dry mouth than with Ditropan.

## **PART I - Study C-95-031: Efficacy and Safety of OROS (oxybutynin chloride) and TTS oxybutynin in Middle-aged and Elderly Women with Urinary Incontinence.**

### **1.0 INTRODUCTORY BACKGROUND**

This Phase 3 study was initially planned as a Phase 2 study. After consultation with the Division, the sponsor was allowed to change the type from Phase 2 to Phase 3. The division requested that the primary analysis be limited to OROS vs. oral placebo instead of the per protocol analysis of OROS vs. combined oral and D-TRANS placebo (Minutes for July 8, 1997 teleconference statistics section states that "it is acceptable that the primary analysis be limited to OROS vs. oral placebo in study C-95-031."). Per the Medical Officer, the main focus of the statistical analysis should be on the primary outcome of the change in the mean change of weekly U-UI episodes from baseline to end of study between the OROS and oral placebo treatment groups.

### **2.0 OBJECTIVES OVERVIEW**

The purpose of this multicenter study conducted in female patients, aged 40 years and older, with urge urinary incontinence (U-UI) was to evaluate the safety and efficacy of OROS as a treatment for U-UI. This was a randomized, double-blind, placebo- and active-controlled, double dummy, parallel-group, fixed dose escalation study.

The primary efficacy objective was to compare the efficacy of OROS and oral placebo in the treatment of female patients with U-UI. The safety objective was to compare side-effect profiles of OROS and oral placebo.

### **3.0 STUDY DESIGN AND PROCEDURES**

Patients were washed out from incontinence medications before starting any study period. Each patient then proceeded through a one week screening period, a one week placebo run-in period, and a 6 week treatment period.

#### **3.1 Screening Period**

The screening period was done to select those patients who had urge urinary incontinence. Subjects were given a patient urinary diary (PUD) to record the time and number of voidings, number of incontinent episodes, and number of incontinent episodes associated with urgency for 7 days. Subjects also underwent several clinical examinations and tests. Those who were diagnosed as urge urinary incontinent and satisfied the inclusion criteria went through the one week placebo run-in period. The main inclusion criteria were:

- Non-pregnant women determined to be in good general health.
- Patients with mixed urinary incontinence, 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.
- Patients were not required to, but could have received previous treatment for U-UI.

- Normotensive, with or without hypertensive medication; no postural hypotension
- Patients who successfully completed the screening urinary diary for seven days.

and the main exclusion criteria were:

- Patients with known genitourinary conditions that may cause incontinence.
- Patients receiving any drugs that are considered effective in the treatment of urinary incontinence less than the equivalent of 5 times the half-life of the drug.
- Patients who have been treated with anticholinergic agents for urge UI and were found to be refractory to these agents.

### 3.2 Placebo Run-In Period

The one week placebo run-in period was done to establish baseline incontinence frequency and urinary frequency and also to qualify patients for randomization. During the run-in period, each patient took one OROS placebo every morning and one IR placebo every 8 hours. Patients recorded in a PUD each void and time of void, each UI episode, and whether the UI episode was associated with urgency for 7 days. Patients proceeded to the treatment period if the run-in PUD reported an average urinary frequency of 10 per 24 hours and at least 7 U-UI episodes per week.

### 3.3 Treatment Period

Following the run-in period, patients were randomized to one of 5 treatment groups: OROS, IR oxybutynin, oral placebo (a combination of IR oxybutynin placebo capsules and OROS placebo tablets), D-TRANS oxybutynin, and D-TRANS placebo. Except for the OROS and oral placebo groups, the other placebo and active treatment groups will not be discussed in detail in this statistical review. Patients were dose titrated to the maximum dose of 15 mg/day over a 6 week period; their dose was increased by 5 mg/day every 2 weeks (Figure A).

Patients recorded each UI episode, whether the UI episode was associated with urgency, and the dosage, date and time that they took all study medications in their PUD. Patients were required to return to the clinic for scheduled weekly visits.

The schedule for administration of active OROS plus IR oxybutynin placebo and oral placebo is presented in Table 3.1. A double-dummy technique was used to carry out the blinding for the oral treatment groups. OROS placebos were identical to OROS in appearance but did not contain active substance. IR oxybutynin placebo tablets were identical in appearance to the IR oxybutynin dosage form but did not contain oxybutynin.

TABLE 3.1  
Treatment Schedule

Treatment	Study Week		
	2-3	4-5	6-7
<b>A</b> OROS & IR placebo	1 (5 mg) OROS qAM 1 IR placebo q8h	2 (5 mg) OROS qAM 2 IR placebos q8h	3 (5 mg) OROS qAM 2 IR placebos q8h
<b>B</b> OROS placebo & IR placebo	1 OROS placebo qAM 1 IR placebo q8h	2 OROS (placebos) qAM 2 IR placebos q8h	3 OROS (placebos) qAM 2 IR placebos q8h

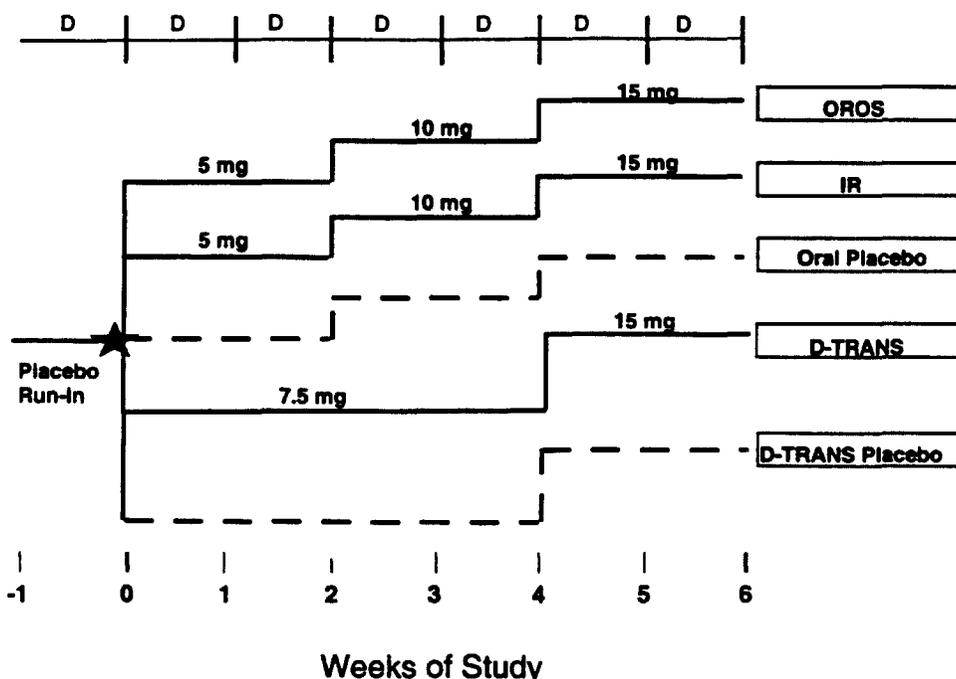
\* N/A = Not applicable

# q8h = a single dose is taken anytime between 7AM and 9PM

@ qAM = 3 separate doses taken: between 7 AM to 9 AM, between 3 PM to 5 PM, and between 9 PM to 12 AM.

Source: Table B, Volume 1.46, page 40.

**Figure A**  
**Study Flow Schema**



D = Patient Urinary Diary  
 OROS = OROS (oxybutynin chloride)  
 IR = IR oxybutynin  
 D-TRANS = D-TRANS oxybutynin

Source: Figure A, Volume 1.46, page 38.

## 4.0 STUDY VARIABLES

### 4.1 Safety Variables

Safety parameters assessed during the study and recorded on safety CRFs included adverse events, anticholinergic side effects, vital signs, standard laboratory tests.

### 4.2 Primary Efficacy Endpoint

The primary efficacy endpoint was the mean change in the number of U-UI episodes per week from baseline to end of study, which was based on the 7-day Patient Urinary Diary (PUD) data. According to the sponsor, a primary efficacy endpoint commonly measured in oxybutynin studies is the change in the number of UI episodes per unit of time from baseline to the end of treatment.

### 4.3 Secondary Efficacy Endpoints

Several secondary efficacy endpoints were assessed using data from the 7 day PUD and patient questionnaires. The per protocol secondary efficacy parameters were as follow:

- 1) Mean incontinence episodes per week (from PUD).
- 2) Mean diurnal and nocturnal micturition frequencies (from PUD).

- 3) Mean incontinence pads changed each day due to wetness (from PUD).
- 4) Mean change of weight of pre-weighted incontinence pads due to wetness.
- 5) Proportion of patients who have less than 6 U-UI episodes per week during follow-up visits.
- 6) Individual score for 5 individual items, each rated using a 5-point category scale, and overall score based on the subjective assessment of urinary symptoms severity (SAUSS) questionnaire evaluated at 1, 2, 3, 4, 5, and 6 week post-treatment.
- 7) Mean voided volume plus post-voided residual volume (PVR) per week evaluated at 1, 2, 3, 4, 5, and 6 week post-treatment.
- 8) Urge to void score in 3 scale categories, detrusor contraction (yes/no), and bladder pressure data based on the cystometric measurements assessed at screening and at end of study.
- 9) Patient satisfaction and overall rating regarding treatment in 5 scale categories assessed at the end of the placebo Run-in period and at end of each 2 week treatment interval.

Secondary outcome results will not be discussed further in this review because the Medical Officer considered them exploratory.

## **5.0 SPONSOR'S STATISTICAL ANALYSIS METHODS**

The following describes the statistical analysis methods as presented by the sponsor in the study report. These methods are per protocol unless otherwise noted.

### **5.1 Analysis Groups and Pooling of Investigators**

All patients randomized into the OROS or oral placebo treatment groups and with available efficacy data were analyzed. The data from centers with less than two evaluable patients per treatment group were pooled into a single center. Any center with evaluable data from two or more patients in each treatment group were represented separately in the efficacy analysis model.

The two treatment groups that were to be used for analysis of the primary efficacy parameter, as requested by the Division, were the OROS and oral placebo groups. The study report presented primary efficacy analysis using three treatment groups: OROS, IR oxybutynin, and oral placebo.

### **5.2 Definition of Baseline and Endpoint Measurements**

Baseline measurements were those taken during the one week run-in period before treatment. Endpoint was defined as the last available measurement up to the end of study during the treatment period regardless whether the patient was on or off study medication. The last 7 days of available PUD data recorded during the treatment period were used to calculate the primary endpoint.

### **5.3 Analysis Methods of the Primary Efficacy Endpoint**

The analysis for the primary efficacy parameter utilized a two-way analysis of variance (ANOVA) model or analysis of covariance (ANCOVA) model. The ANOVA model included treatment, center, and treatment by center interaction factors. The ANCOVA model included treatment, center, and treatment by center interaction factors, and baseline number of U-UI episodes per week collected during the placebo run-in period as the covariate.

The final ANOVA/ANCOVA model was selected from a series of ANOVA/ANCOVA models, using the change from baseline measurements as the dependent variable. The model selection process was based on the procedure found in Milliken & Johnson [Analysis of Messy Data, Vol.

III (manuscript). Kansas State University, Department of Statistics, 1989]. The procedure for determining the form of the ANOVA/ANCOVA model was as follows:

- a) Test the hypothesis that the slopes are zero at significance level = 0.10.
  - i) If fail to reject, compare the treatment using analysis of variance
  - ii) If reject, go to b).
- b) Test the hypothesis that the slopes are equal at significance level = 0.10 (interaction effects testing).
  - i) If fail to reject, use a parallel lines model and compare the treatments by comparing the intercepts or adjusted means (least squares means).
  - ii) If reject, go to c).
- c) Use the unequal slope model and present analysis results at three covariate values: Overall covariate mean, 25<sup>th</sup> percentile, and 75<sup>th</sup> percentile of the covariate values.

The least squares estimate and a 95% confidence interval of the mean difference between the two treatments in the change in number of U-UI episodes per week were constructed. All tests for treatment comparisons were performed at the 0.05 significance level. All statistical tests performed were two-sided.

## 6.0 STUDY HYPOTHESIS AND SAMPLE SIZE

As requested by the Division (Section 1.0), the following null hypothesis was tested:

*The treatment difference in the mean change in the number of U-UI episodes per week from baseline to last week of treatment between the OROS group and the oral placebo group was equal to zero.*

The sponsor stated that a sample size of at least 120 evaluable patients with U-UI would provide 80% power to detect a difference of 10 episodes in the change in U-UI episodes per week between oxybutynin-treated groups and placebo groups. The change was from baseline to last week of treatment. The sample size was based on a two-sample t-test with standard deviation of 11 episodes per week, a 2 to 1 enrollment ratio of active to placebo treatments (30 patients in each of the 3 active groups and 15 patients in each of the 2 placebo groups) and 0.05 significance level. To allow for a 30% dropout rate, an enrollment of 176 patients was planned.

## 7.0 OTHER STUDY INFORMATION

### 7.1 Principal Investigators

Table 7.1 presents the 9 sites that participated in study C-95-031. There were 9 principal investigators and many subinvestigators.

**Table 7.1**  
**Principal Investigators for Study C-95-031**

Principal Investigator	Number of Subinvestigators	Number of Study locations
Brito CG	5	1 in Phoenix, AZ
Klimberg I	3	3 in Summerfield and Ocala, FL
Knoll D	4	1 in Nashville, TN
McMurray J	2	2 in Huntsville, AL
Schmidt RA	0	1 in Denver, CO
Steidle C	3	1 in Fort Wayne, IN
Susset J	0	1 in Providence, RI
Tuttle J	1	1 in Lexington, KY
Zinner N	4	2 in Torrance, CA

### 7.2 Patient Enrollment and Randomization

Table 7.2 presents the number of patients enrolled and randomized by each study site. A total of 134 patients with U-UI were enrolled. The active treatment groups were 34 patients on OROS, 32 patients on IR oxybutynin, and 35 patients on D-TRANS oxybutynin. The placebo treatment groups were 16 patients on oral placebo and 17 patients on D-TRANS placebo. The protocol stated that at least 120 evaluable patients would be enrolled.

**Table 7.2**  
**Number of Patients Enrolled and Randomized by Investigator**

Study Site (Principal Investigator)	Number of Subjects Enrolled (Completed) (N=134)	Randomized to OROS (n=34)	Randomized to Oral Placebo (n=16)	Randomized to the Other 3 Groups (n=84)
1 (Brito)	6 (4)	2	2	2
2 (Klimberg)	13 (9)	3	4	6
3 (Knoll)	13 (9)	3	2	8
4 (McMurray)	7 (7)	2	2	3
5 (Schmidt)	15 (12)	4	4	7
6 (Steidle)	5 (4)	1	0	4
7 (Susset)	33 (29)	8	8	17
8(Tuttle)	25 (25)	6	6	13
9 (Zinner)	17 (17)	5	4	8

### 7.3 Patient Accountability and Evaluability

Table 7.3 displays the disposition of the enrolled patients and the number of patients evaluable for the efficacy and safety analyses. Of the 34 patients randomized to OROS, 32 completed the study. Of the 16 patients randomized to oral placebo, 15 completed the study. The one patient (Subject ) who did not complete the study due to an adverse event was treated with 5 mg/day of oral placebo. All other patients were treated at the final dose of 15 mg/day. None of the patients in the OROS or oral placebo groups discontinued study because of report of dry

mouth. The dropout rates were similar for both groups 5.9% (2/34) for OROS and 6.2% (1/16) for oral placebo.

**Table 7.3**  
**Patient Accountability**

Disposition	OROS	Oral Placebo
Number Enrolled	34	16
Number Evaluable for Safety	34	16
Number Completed Study	32	15
Number Who Did Not Complete Study	2	1
Reason for Discontinuation		
Personal Reason*	2	
Adverse Event**		1
Number of Patients Evaluable for Efficacy	32	15

\* Patient numbers : both in OROS group  
 \*\* Patient number Oral Placebo group

## 8.0 SPONSOR'S RESULTS

### 8.1 Primary Efficacy Results

The final model for the analysis of the primary efficacy parameter was a two-way ANCOVA model with treatment, center, treatment-by-center interaction factors and baseline weekly U-UI episodes as the covariate. The model included data from the three oral treatment groups: OROS, IR oxybutynin, and oral placebo. Since 5 of the 9 study sites had less than two evaluable patients per treatment group, they were pooled into a single center, as per protocol. These were the sites whose Principal Investigators were Brito, Klimberg, McMurray, Schmidt, and Steidle.

The results of this analysis are presented in Table 8.1. OROS was more effective than placebo in reducing the number of weekly U-UI episodes from baseline ( $p=0.001$ ).

**Table 8.1**  
**Primary Efficacy Results**

	No. of U-UI episodes/week
Adjusted mean (SEM) change from baseline:	
OROS (n=34)	-18.6 (1.5)
Oral Placebo (n=16)	-10.2 (2.0)
Adjusted Mean Difference in Change:	
OROS-Oral Placebo (SEM)	-8.4 (2.5)
95% Confidence Interval for Difference	(-13.4, -3.5)
OROS vs Oral Placebo p-value	0.001

From ANCOVA model using OROS, OROS placebo, and IR oxybutynin groups.

## 8.2 Safety Results

No death or serious adverse events were noted in study C-95-031 per the Medical Reviewer. For further safety information, refer to the Medical Reviewer's safety review.

## 9.0 REVIEWER'S COMMENTS ON STUDY DESIGN AND ANALYSES

1. The Division requested that the primary efficacy analysis be conducted using only the OROS and oral placebo treatment groups. The minutes for the for July 8, 1997 teleconference statistics section stated that:

*"... it is acceptable that the primary analysis be limited to OROS vs. oral placebo in study C-95-031."*

Per the Medical Officer, the main focus of the primary efficacy analysis needed to demonstrate that OROS could beat placebo. Instead, the sponsor conducted the primary efficacy analysis using the three oral treatment groups (OROS, IR oxybutynin, and oral placebo). The statistical reviewer performed the analysis requested by the Division and results are presented in Section 10.0.

2. The sponsor did not present a race subgroup analysis of the primary efficacy endpoint. An age (<65 years, ≥65 years) subgroup analysis for the unadjusted primary efficacy endpoint was presented. The difference in the change from baseline in the number of weekly urge urinary incontinence episodes was similar in the two age groups. Since all the patients were female, a subgroup analysis by gender was not warranted.

## 10.0 STATISTICAL REVIEWER'S ANALYSES AND RESULTS

For each patient, the value of the baseline and endpoint number of weekly U-UI episodes were verified to have been calculated using per protocol definition. For baseline, it was the sum of the number of U-UI episodes during the 7 day run-in period and for endpoint it was the sum of the number of U-UI episodes during the last 7 days on treatment.

All 50 patients had complete baseline data, i.e., they had data for all 7 days of the run-in period. For the treatment period, 2 patients had 6 days worth of data and one patient had 5 days worth of data. For these patients, the number of U-UI episodes for each of the missing days was imputed using the following procedure:

Take the sum of the number of U-UI episodes for the available days of data divided by the number of available days of data and round to the closest integer.

This procedure was reasonable to use, per the Medical Officer, since urge urinary incontinence is a highly variable condition on a day to day basis. Preserving the actual number of U-UI episodes for the days where data was available was important in reflecting this variability.

Only one patient's baseline data value did not correspond to what the statistical reviewer calculated (See Appendix 1). This patient had complete baseline data. All other data values corresponded to what the statistical reviewer calculated.

The statistical reviewer's analysis used the same procedure the sponsor used and described in Section 5.3. The final two-way ANCOVA model had treatment, center, treatment-by-center

interaction factors and baseline weekly U-UI episodes as the covariate. A two-way ANOVA model with treatment, center, treatment-by-center interaction factors was also fit to the baseline weekly U-UI episode data. Five of the 9 study sites were pooled into a single center, as done by the sponsor and per protocol.

The statistical reviewer conducted a separate analysis of the primary efficacy data using only the OROS and oral placebo groups. This was done because the Division requested this analysis from the sponsor (See Section 1.0). The results of this analysis are presented in Table 10.1. The result was that OROS was more effective than placebo in reducing the number of weekly U-UI episodes from baseline ( $p=0.004$ ).

**Table 10.1**  
**Primary Efficacy Results**

	No. of U-UI episodes/week
Adjusted Mean Baseline:	
OROS (n=34)	16.0
Oral Placebo (n=16)	19.8
Adjusted Mean (SD) Change from Baseline:	
OROS	-15.8 (8.9)
Oral Placebo	-7.6 (8.6)
Adjusted Mean Difference in Change:	
OROS-Oral Placebo	-8.2
95% Confidence Interval for Difference	(-13.6, -2.8)
OROS vs Oral Placebo p-value	0.004

From ANOVA and ANCOVA models using OROS and OROS placebo groups.

## 11.0 REVIEWER'S RECOMMENDATION

From a statistical standpoint, the sponsor has provided an adequate and well controlled study that shows evidence for efficacy in support of their intended objective to demonstrate the superiority of OROS over placebo in the treatment of urge urinary incontinence based on the endpoint of the difference in the change from baseline of the number of urge urinary incontinence episodes per week.

**PART II - Study C-95-049: 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).**

### **1.0 INTRODUCTORY BACKGROUND**

This Phase 3 study was initially planned as a Phase 2 study. After consultation with the Division, the sponsor was allowed to change the type from Phase 2 to Phase 3. The Division felt that OROS oxybutynin and Ditropan immediate release (IR) oxybutynin may be "similar" drugs, the difference being in their formulations: Ditropan is an immediate release drug while OROS is an extended release drug. The Medical Officer recommended that an absolute difference of no more than 4 U-UI episodes per week for the absolute difference in the change from baseline between OROS and Ditropan would be considered clinically acceptable as "therapeutically equivalent."

### **2.0 OBJECTIVES OVERVIEW**

The purpose of this multicenter study conducted in male and female patients, aged 40 to 75 years, with urge urinary incontinence (U-UI) or mixed urinary incontinence was to determine the minimum effective dose (MED) and maximum tolerated dose (MTD) for each patient for the OROS and Ditropan treatment groups. This was a randomized, double-blind, placebo- and active-controlled, double dummy, parallel-group, dose-escalation study.

The primary efficacy objective was to demonstrate the therapeutic equivalence of OROS and Ditropan in the treatment of patients with urge or mixed urinary incontinence at the MED or MTD or at the maximum dose allowed under the protocol. Additional objectives were to compare the efficacy, safety and anticholinergic effects profile of OROS to Ditropan.

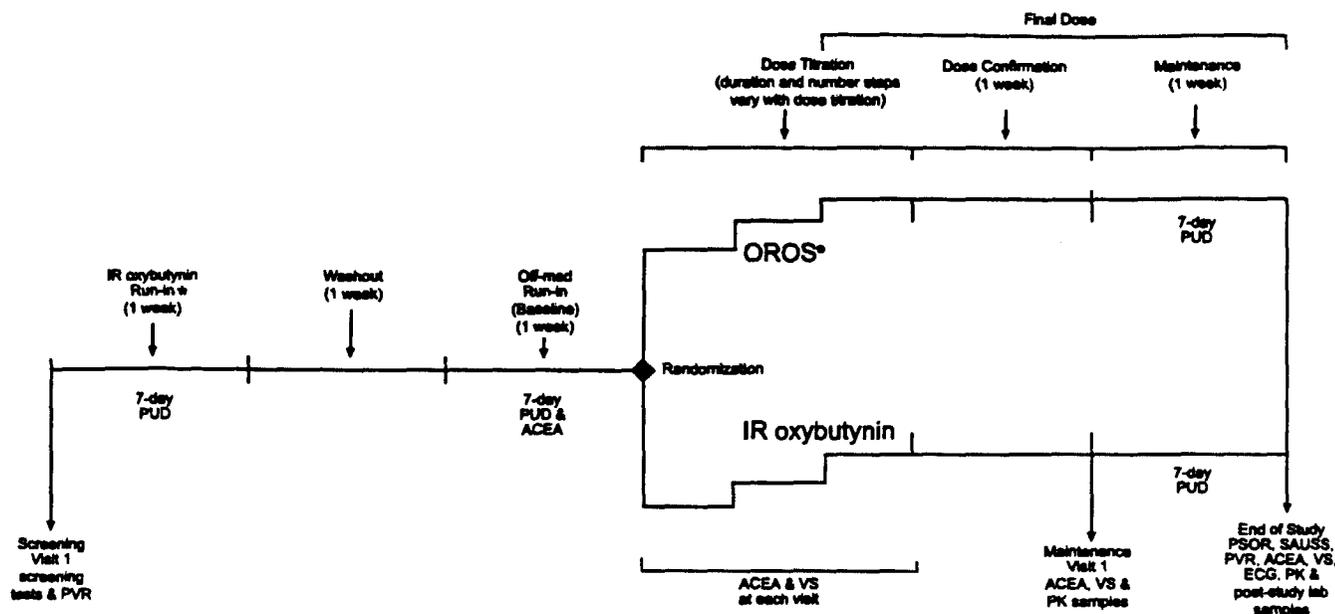
### **3.0 STUDY DESIGN AND PROCEDURES**

Patients were washed out from incontinence medications before starting the study run-in period. Screening for study included a one week therapeutic responder screening trial for some patients and a study screen for all patients. Each patient then proceeded through a one week run-in period, a greater than 2 week treatment period, and a one week maintenance period (Figure B).

#### **3.1 Therapeutic Responder Screening Trial**

Patients who did not have prior treatment for their urge UI and for whom Ditropan would be a reasonable therapeutic alternative entered a one week, therapeutic trial period of Ditropan. Patients who appeared to be responders returned to the study site and completed the study screening procedure; non-responders were screening failures.

**Figure B  
Study Overview**



\* Only patients taking Ditropan before study enrollment entered this IR Oxybutynin Run-in. All other patients started the study in the Washout Period.

Abbreviations: ACEA=Anticholinergic Effects Assessment questionnaire; ECG=electrocardiogram; MAD=maximum allowable dose; MED=minimum effective dose; MTD=maximum tolerated dose; PK=pharmacokinetic; PSOR=Patient Satisfaction and Overall Rating questionnaire; PUD=Patient Urinary Diary; PVR=post-void residual; SAUSS=Subjective Assessment of Urinary Symptom Severity questionnaire; VS=orthostatic vital signs

Source: Figure A, Volume 1.58, page 43.

### 3.2 Study Screening Procedure

All potential subjects underwent a screening procedure that included several clinical examinations and tests. Once a subject was successfully screened and satisfied the inclusion criteria, they entered the run-in period. The main inclusion criteria were:

- Men and non-pregnant women determined to be in good health, with urge or mixed UI provided that stress UI is not the predominant manifestation of mixed UI.
- Patients who were currently taking immediate release Ditropan, Levsin, or Probanthine, or who have taken Ditropan in the past for urge or mixed UI. Patients who have taken Ditropan for urge or mixed UI, but who discontinued the medication should have discontinued due to anticholinergic effects and not due to failure of efficacy.
- Patients who did not previously take Ditropan, Levsin, or Probanthine as treatment for urge UI who participated in a therapeutic responder screening trial of Ditropan.
- Patients who were able to differentiate incontinent episodes associated with urgency from incontinent episodes not associated with urgency.
- Normotensive, with or without hypertensive medication; no postural hypotension.

and the main exclusion criteria were:

- Patients with known genitourinary conditions that may cause incontinence.
- Patients with glaucoma or untreated narrow anterior chamber angles, obstructive bowel disease or severe narrowing of the gastrointestinal tract, obstructive uropathy, or myasthenia gravis.
- Patients receiving any drugs other than Ditropan, Levsin, Cystospaz, or Probanthine that are considered effective in the treatment of urge urinary incontinence.

- Patients who had been treated with anticholinergic agents for urge UI and were found to be refractory to these agents.
- Patients who have taken an investigational drug (except for oxybutynin) within a period of one month or 5 times the half-life of the drug. Patients who took OROS as an investigational formulation under ALZA protocol C-95-031 could be enrolled.

### **3.3 Run-In Period**

The one week run-in period was done to establish baseline incontinence frequency and urinary frequency and also to qualify patients for randomization. No treatment was taken during this period. Patients recorded in a patient urinary diary (PUD) each void and time of void, each UI episode, and whether the UI episode was associated with urgency for 7 days. The patient proceeded to the treatment period if they had at least six urge UI episodes per week recorded on the run-in PUD.

### **3.4 Treatment Period**

Following the run-in period, patients were randomized equally into one of the two treatment groups: OROS and Ditropan. The purpose of the Treatment Period, which lasted from 1 to 9 weeks, was to determine the MED and/or MTD for each patient. The MED was defined as the dose at which the patient reported no U-UI episodes during the last 2 days of the 4 to 7 day dosing interval. The MTD was defined as the highest dose at which the patient did not experience one or more intolerable anticholinergic effects. Continence and anticholinergic side effects were recorded by the patient in a weekly PUD.

Both Ditropan and OROS were over-encapsulated with identical capsules for the purpose of blinding and packaged on daily dosing cards. Placebo capsules were identical to those used to over-encapsulate Ditropan and OROS but did not contain oxybutynin. To maintain blinding, placebo capsules were included on the cards as necessary to maintain comparable dosing schedules for the OROS and Ditropan groups.

Patients began OROS or Ditropan at a dose of 5 mg/day and were dose-titrated in 5 mg increments to a therapeutic response, limited by the development of intolerable anticholinergic side effects, up to the maximum allowable dose (30 mg/day of OROS or 20 mg/day of Ditropan). The patient's dose was increased or decreased or the patient was dropped from the study by the investigator using a prospectively described set of decision rules. Following the Treatment Period the patient entered the Maintenance Period.

### **3.5 Maintenance Period**

During the one week maintenance period, patients received therapy at dose established during the treatment period. Patients received either one to four Ditropan 5 mg capsules per day (5 mg per day to 5 mg four times per day), or one to six OROS 5 mg capsules per day (5 mg/day to 30 mg/day) as a single AM dose. The patient recorded each time they voided, each incontinent episode, and whether the incontinent episode was associated with urgency in a PUD for 7 days.

New medication cards were distributed and used ones were collected by the investigator at each clinical visit. Each card contained the medication for one day and the times at which the medication was to be taken. Patient compliance was monitored by examining the returned used and unused dosage cards and recording missed doses on the Daily Dosing Record CRF.

## **4.0 STUDY VARIABLES**

### **4.1 Safety Variables**

Safety parameters assessed during the study and recorded on safety CRFs included adverse events, anticholinergic side effects, vital signs, standard laboratory tests.

### **4.2 Primary Efficacy Endpoint**

The primary efficacy parameter was the mean change in the number of U-UI episodes per week from baseline to last week maintenance therapy based on the Patient Urinary Diary (PUD).

### **4.3 Secondary Efficacy Endpoints**

Several secondary efficacy parameters were assessed using data from the 7 day PUD and two patient questionnaires. The per protocol secondary efficacy parameters were as follow:

- 1) Mean change of urge incontinence episodes per week from the week that the patient recorded the Run-In diary while on Ditropan to the week of maintenance therapy at the MTD, MTD, or maximum dose.
- 2) Mean urge incontinence episodes per week.
- 3) Mean diurnal and nocturnal micturition frequencies.
- 4) Individual score in five scale categories for five individual items and overall score based on the subjective assessment of urinary symptom severity (SAUSS) questionnaire.
- 5) Individual score for 4 individual items and overall score, each rated using a 5-point category scale, regarding treatment based on the patient satisfaction and overall rating (PSOR) questionnaire evaluated at the end of maintenance therapy at the MED, MTD, or maximum dose.
- 6) Mean void volume plus post-void residual volume from pre-dosing to end of maintenance therapy at the MED, MTD, or maximum dose.
- 7) Individual score of subject assessment of anticholinergic effects (ACEA).

Secondary outcome results will not be discussed further in this review because the Medical Officer considered them exploratory.

## **5.0 SPONSOR'S STATISTICAL ANALYSIS METHODS**

The following describes the statistical analysis methods as presented by the sponsor in the study report. These methods are per protocol unless otherwise noted.

### **5.1 Analysis Groups and Pooling of Investigators**

All randomized patients with evaluable baseline and endpoint data were included in the efficacy analyses. The analysis of the primary efficacy parameter was an intent-to-treat analysis, which included all randomized patients with available data. The data from investigational centers with less than two evaluable patients per treatment group were pooled into a single center. Any center with evaluable data from two or more patients in each treatment group were represented separately in the model for efficacy analysis.

### **5.2 Definition of Baseline and Endpoint Measurements**

Baseline measurements were those taken during the one week run-in period before the treatment period. The endpoint was defined as the last available measurement up to the end of study during the maintenance period regardless whether the patient was on or off study medication. The last 7 days of available PUD data recorded during the maintenance were used to calculate

the primary endpoint. For patients who had less than 7 days PUD data, weekly PUD measurements were normalized to 7 days to derive the baseline and endpoint values.

### **5.3 Analysis Methods of the Primary Efficacy Parameter**

A two-way analysis of variance (ANOVA) model or analysis of covariance (ANCOVA) model was used for the analysis of the primary efficacy parameter. The ANOVA model was to include treatment, center, and treatment by center interaction factors. The ANCOVA model was to include treatment, center, and treatment by center interaction factors, and baseline number of U-UI episodes per week collected during the run-in period as the covariate. The final ANCOVA model was selected from a series of ANCOVA models using the same model selection process as described in PART I, Section 5.3.

The least squares estimate and 95% confidence interval of the mean difference between the two treatment groups in the mean change in the number of weekly U-UI episodes from baseline to the maintenance period were calculated. The primary efficacy analysis was the 95% confidence interval of treatment difference, rather than a formal hypothesis test. The two treatments would be considered therapeutically equivalent if the 95% confidence interval of the difference in the mean reduction of U-UI episodes per week was within  $\pm 4$  episodes.

## **6.0 STUDY HYPOTHESIS AND SAMPLE SIZE**

Initially, the sponsor wanted to test the following null hypothesis:

*The treatment difference between the OROS and Ditropan groups in the change in U-UI episodes per week from baseline to end of study was equal to zero.*

After changing the initial Phase 2 nature of the study to a Phase 3 study, the sponsor decided to test for the therapeutic equivalence of OROS and Ditropan.

The sponsor stated that a sample size of 80 patients with urge or mixed UI would provide 80% power to detect a difference of 4 episodes in the mean change of number of UI episodes per week between OROS and Ditropan, assuming a standard deviation of 6 episodes per week for each group, a two-sample t-test, and significance level of 0.05. To allow for a 20% dropout rate, an enrollment of approximately 100 patients was planned.

The sponsor also claimed that this sample size of 80 patients would provide 80% probability to demonstrate therapeutic equivalence between the OROS and Ditropan treatments. This was based on two one-sided tests with significance level of 0.025, assuming a mean reduction of 10 U-UI episodes per week and a standard deviation of 6 episodes per week for each treatment.

## **7.0 OTHER STUDY INFORMATION**

### **7.1 Principal Investigators**

Table 7.1 presents the 13 sites that participated in study C-95-049. There were 13 principal investigators and many subinvestigators.

**Table 7.1**  
**Principal Investigators for Study C-95-049**

Principal Investigator	Number of Subinvestigators	Number of Study locations
Anderson RU	1	1 in Stanford, CA
Auerbach S	0	1 in Newport Beach, CA
Blank B	9	2 in Portland, OR
Brito CG	5	1 in Phoenix, AZ
Brown JS	2	2 in San Francisco, CA
Duckett MJ	1	1 in Baltimore, MD
Dula E	2	2 in West Hills and Van Nuys, CA
Kaufman JM	3	3 in Aurora, CO
Mobley DF	2	2 in Houston, TX
Murdock M	2	1 in Greenbelt, MD
Saltzstein D	4	2 in San Antonio, TX
Susset J	1	1 in Providence, RI
Weems L	8	2 in Jackson, MS

## 7.2 Patient Enrollment and Randomization

Table 7.2 presents the number of patients enrolled and randomized by each study site. A total of 105 male and female patients were enrolled. These patients were randomized into one of two double-blind treatment groups, 53 patients in the OROS group and 52 in the Ditropan group. Of these 105 patients, 66 (62.9%) were known to be responders prior to screening and 39 (37.1%) were confirmed to be responders during the therapeutic responder screening trial.

**Table 7.2**  
**Number of Patients Enrolled and Randomized by Investigator**

Study Site (Principal Investigator)	Number of Subjects Enrolled (Completed) (N=105)	Randomized to OROS (n=53)	Randomized to Ditropan (n=52)
1 (Anderson)	3 (3)	1	2
2 (Auerbach)	9 (9)	5	4
3 (Blank)	11 (7)	5	6
4 (Brito)	1 (1)	1	0
5 (Brown)	23 (23)	12	11
6 (Duckett)	1 (1)	0	1
7 (Dula)	5 (5)	3	2
8 (Kaufman)	7 (6)	4	3
9 (Mobley)	14 (12)	7	7
10 (Murdock)	6 (5)	3	3
11 (Saltzstein)	9 (8)	4	5
12 (Susset)	7 (7)	3	4

13 (Weems)	9 (5)	5	4
------------	-------	---	---

### 7.3 Patient Accountability and Evaluability

Table 7.3 displays the disposition of the enrolled patients and the number of patients evaluable for the efficacy and safety analyses. This study had few patients who dropped out [12.4% (13/105)]. Of the 53 patients randomized to OROS, 46 completed the study. Of the 52 patients randomized to Ditropan, 46 completed the study. The dropout rates were similar for both groups: 13.2% (7/53) for OROS and 11.5% (6/52) for Ditropan.

Of the 10 who discontinued study medication prematurely due to adverse event(s), 3 reported dry mouth (Subject in OROS group and Subject and in Ditropan group). Thus, this study had very few patients who dropped out when they reported dry mouth (3/105= 2.9%).

**Table 7.3**  
**Patient Accountability**

Disposition	OROS	Ditropan
Number Enrolled in OROS and Oral Placebo Groups	53	52
Number Evaluable for Safety	53	52
Number Completed Study	46	46
Number Who Did Not Complete Study	7	6
Reason for Discontinuation		
Personal Reason*	1	1
Adverse Event**	5	5
Protocol Deviation***	1	
Number of Patients Evaluable for Efficacy	46	46
* Patient numbers (OROS) and (Ditropan)		
** Patient numbers (OROS) and (Ditropan)		
*** Patient number (OROS)		

## 8.0 SPONSOR'S RESULTS

### 8.1 Primary Efficacy Results

The final model for the analysis of the primary efficacy parameter was a two-way ANCOVA model with treatment, center, treatment-by-center interaction factors and baseline weekly U-UI episodes as the covariate. Since 3 of the 13 study sites had less than two evaluable patients per treatment group, they were pooled into a single center, as per protocol. These were the sites whose Principal Investigators were Anderson, Brito, and Duckett. Seven patients in the OROS group and 5 in the Ditropan group did not have maintenance PUD data and were excluded from the analysis of the primary efficacy parameter.

The results of this analysis are presented in Table 8.1. The sponsor concluded that "OROS was comparable to Ditropan in reducing the number of weekly U-UI episodes ( $p=0.636$ )."

**Table 8.1**  
**Primary Efficacy Results**

	No. of U-UI episodes/week
Adjusted mean (SEM) change from baseline:	
OROS (n=46)	-20.7 (1.3)
Ditropan (n=47)	-21.6 (1.3)
Adjusted Mean Difference in Change:	
OROS-Ditropan (SEM)	-0.9 (1.9)
95% Confidence Interval for Difference	(-2.8, 4.6)
OROS vs Ditropan p-value	0.636

From ANCOVA model using OROS and Ditropan groups.

## 8.2 Safety Results

No death was noted but one serious adverse event occurred in a patient (Subject ) in the Ditropan group during the study treatment period in Study C-95-049 per the Medical Officer. For further safety information, refer to the Medical Reviewer's safety review.

## 9.0 REVIEWER'S COMMENTS ON STUDY DESIGN AND ANALYSES

1. The one week maintenance period in this study did not provide an adequate length of time to demonstrate a realistic efficacy outcome for this chronic use drug. From minutes of the February 28, 1997 internal meeting, the Medical Reviewer stated the following:

The minimum time the patients are on the drug to assess efficacy is one week; this is not sufficient time to demonstrate efficacy for a Phase 3 trial of a drug with a chronic use indication.

Thus, care should be taken when interpreting the results of this trial as a longer term result would have provided more realistic information about the performance of each treatment.

2. This is an "enriched" study since only those patients who responded to oxybutynin or other anticholinergic medications were enrolled. This enrichment should be taken into account when interpreting the study results because they are enhanced and cannot be generalized to patients with a diagnosis of urge urinary incontinence.

3. For patients who had less than 7 days of PUD data, the sponsor normalized the weekly PUD measurements to 7 days to derive the baseline and endpoint values by the sponsor. This normalization procedure was not described by the sponsor in the protocol or study report.

4. The sponsor concluded that OROS was comparable to Ditropan in reducing the number of weekly U-UI episodes per week. Statistically, this conclusion is borderline since the 95% confidence interval of (-2.8, 4.6) episodes per week did not fall within the *a priori* confidence interval limits for demonstrating therapeutic equivalence of  $\pm 4$  episodes per week.

5. Two of the 13 (23%) principal investigators who participated in this study (C-95-049) also participated in study C-95-031. The principal investigators and subinvestigators who participated in both studies are presented in Table 9.1.

**Table 9.1  
Principal Investigators Who Participated in Multiple Studies**

Principal Investigator	Subinvestigators	Study Numbers
Brito CG	Argueso LR, Bailey RB, Bans LL, Bohnert W, Zeidman EJ	C-95-031 C-95-049
Susset J	None	C-95-031 C-95-049

Using the same principal investigators and subinvestigators in more than one Phase 3 clinical trial violates the regulatory requirement of independent studies. Independence minimizes bias in study results that may be due to the study conduct.

6. The Division requested an intent-to-treat analysis be conducted for the primary efficacy analysis. No ITT analyses were performed by the sponsor or presented in the study report. The sponsor stated in the protocol (Volume 1.60, page 79) that:

For the analysis of the primary efficacy parameter, the main analysis will be an intent-to-treat analysis, which includes all randomized patients with available data.

while in the study report the sponsor stated that:

For the primary and secondary efficacy parameters, the main analysis included all randomized patients with available baseline and endpoint data.

This second analysis, which is not an ITT analysis but an efficacy evaluable or completer's analysis, was reported in the submission.

7. The sponsor did not present efficacy subgroup analyses for gender, age, and race.

## **10.0 STATISTICAL REVIEWER'S ANALYSES AND RESULTS**

For each patient, the value of the baseline and endpoint number of weekly U-UI episodes were verified to have been calculated using per protocol definition. For baseline, it was the sum of the number of U-UI episodes for the last 7 days on baseline and for maintenance endpoint it was the sum of the number of U-UI episodes for the last 7 days of maintenance.

All but 8 patients had complete baseline data, i.e., they had data for all 7 days of the run-in period. Of these 8, three had 5 days worth of data and five had 6 days worth of data. For the maintenance period, one patient had 2 days worth of data (Subject had an adverse event and then stopped study) and six patients had 6 days worth of data. For these patients, the number of U-UI episodes for each of the missing days was imputed using the following procedure:

Take the sum of the number of U-UI episodes for the available days of data divided by the number of available days of data and round to the closest integer.

This procedure was reasonable to use, per the Medical Officer, since urge urinary incontinence is a highly variable condition on a day to day basis. Preserving the actual number of U-UI episodes for the days where data was available was important in reflecting this variability.

Five patients' baseline data value did not correspond to what the statistical reviewer calculated (See Appendix 1). Four of these five patients had complete maintenance data. -All other data values corresponded to what the statistical reviewer calculated.

The statistical reviewer's analysis used the same procedure the sponsor used and described in PART I, Section 5.3. The final two-way ANCOVA model had treatment, center, treatment-by-center interaction factors and baseline weekly U-UI episodes as the covariate. A two-way ANOVA model with treatment, center, treatment-by-center interaction factors was also fit to the baseline weekly U-UI episode data. Three of the 13 study sites were pooled into a single center, as done by the sponsor and per protocol.

The statistical reviewer conducted a separate analysis of the primary efficacy data using all randomized patients utilizing the last-value-carried-forward ITT technique to account for those patients who did not have maintenance data. This was done because the Division requested this analysis from the sponsor (See Section 9.0, item 7). The results of this analysis are presented in Table 10.1. The result was that OROS was not therapeutically equivalent to Ditropan in reducing the number of weekly U-UI episodes from baseline. The 95% confidence interval of (-2.9, 6.4) episodes per week did not fall within the *a priori* confidence interval of (-4, 4) episodes per week to demonstrate therapeutic equivalence.

**Table 10.1**  
**Primary Efficacy Results**

	No. of U-UI episodes/week
Adjusted Mean Baseline:	
OROS (n=53)	27.2
Ditropan (n=52)	21.3
Adjusted Mean (SD) Change from Baseline:	
OROS	-17.9 (11.9)
Ditropan	-19.6 (11.9)
Adjusted Mean Difference in Change:	
OROS-Ditropan	1.7
95% Confidence Interval for Difference	(-2.9, 6.4)
OROS vs Ditropan p-value	0.466

From ANOVA and ANCOVA models using OROS and Ditropan groups.

## 11.0 REVIEWER'S RECOMMENDATION

From a statistical standpoint, the sponsor has provided an adequate and well controlled study that did not show evidence for efficacy in support of their intended objective to demonstrate the therapeutic equivalence of OROS to Ditropan in the treatment of urge urinary incontinence as measured by no more than a 4 episode difference in the change from baseline of the weekly number of urge urinary incontinence episodes.

**PART III - Study C-97-020: Comparison of Dry Mouth during Treatment with OROS (oxybutynin chloride) and Ditropan in Patients with Urge Urinary Incontinence.**

## **1.0 INTRODUCTORY BACKGROUND**

The Division required that the study demonstrate the therapeutic equivalence of OROS and Ditropan first before claiming less dry mouth for OROS. The Medical Officer recommended that an absolute difference of no more than 4 U-UI episodes per week for the difference in the change from baseline between OROS and Ditropan would be considered clinically acceptable as "therapeutically equivalent."

## **2.0 OBJECTIVES OVERVIEW**

The purpose of this multicenter study conducted in male and female patients, aged 40 to 75 years, with urge urinary incontinence (U-UI) or mixed urinary incontinence was to compare the difference in dry mouth in patients treated with OROS and Ditropan for U-UI. This was a randomized, double-blind, placebo- and active-controlled, double dummy, parallel-group, dose-titration study.

The primary study objective was to demonstrate that the incidence of dry mouth was less for those patients taking OROS compared to Ditropan in patients treated for urge urinary incontinence (U-UI). Additional objectives were to compare the efficacy, quality of life, patient satisfaction and safety of OROS and Ditropan.

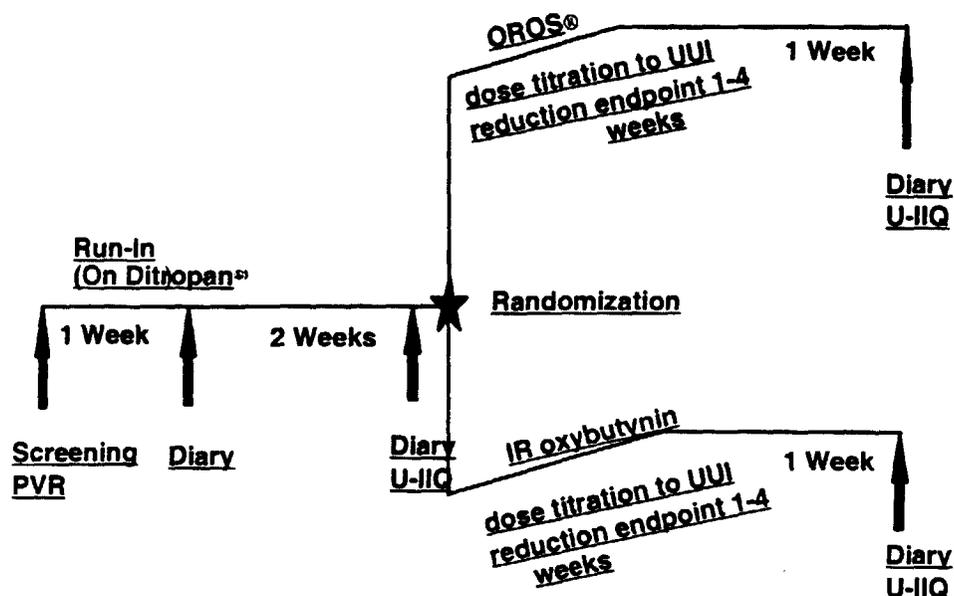
## **3.0 STUDY DESIGN AND PROCEDURES**

Patients were washed out from incontinence medications before starting any study period. Screening for study included a one week therapeutic responder screening trial for some patients and a study screen for all patients. Each patient then proceeded through a two week run-in period, up to a 4 week dose-titration period, and a one week maintenance period (Figure C). At each clinic visit, patients were questioned about the occurrence of any unusual symptoms or adverse events since the last clinic visit. Any anticholinergic effects, any unusual symptoms or adverse events were recorded on the Adverse Events CRF.

### **3.1 Therapeutic Responder Screening Trial**

Patients who did not have prior treatment for their urge UI and for whom Ditropan would be a reasonable therapeutic alternative entered a one week, therapeutic trial period of Ditropan. Patients who appeared to be responders returned to the study site and completed the study screening procedure; non-responders were screening failures.

**Figure C**  
**Study Flow Schema**



Source: Figure A, Volume 4.6, page 39.

### 3.2 Study Screening Procedure

All potential subjects underwent a screening procedure that included several clinical examinations and tests. Once a subject was successfully screened and satisfied the inclusion criteria, they entered the run-in period. The main inclusion criteria were:

- Men and non-pregnant women determined to be in good health, with urge UI or mixed UI with urge UI as the major component.
- Patients who either were currently taking Ditropan, Levsin, Probanthine or other anticholinergic medication for treatment of U-UI; had taken anticholinergic medication for U-UI in past but discontinued for reasons other than lack of efficacy; or were therapeutic responders from the Ditropan Therapeutic Responder Trial.
- Patients who were able to differentiate incontinent episodes associated with urgency from incontinent episodes not associated with urgency.
- Normotensive, with or without hypertensive medication; no postural hypotension.

and the main exclusion criteria were:

- Patients with known genitourinary conditions that may cause incontinence.
- Patients with glaucoma or untreated narrow anterior chamber angles, obstructive bowel disease or severe narrowing of the gastrointestinal tract, obstructive uropathy, myasthenia gravis, unstable diabetes, or unstable cardiovascular status.
- Patients with clinically significant medical problems or other organ abnormality or pathology for whom, in the opinion of the investigator, administration of oxybutynin chloride would present undue risk.
- Patients who had been treated with anticholinergic agents for urge UI and were found to be refractory to these agents.
- Patients who have taken an investigational drug within a period of one month or five times the half-life of the drug (whichever is longer). Patients who have taken oxybutynin chloride as an investigational formulation under ALZA protocols C-95-031, C-95-049 and C-96-070 may be enrolled into this study.

### 3.3 Run-In Period

The run-in period lasted 2 weeks. The first week was a washout period and the second week was done to establish baseline incontinence frequency and urinary frequency and also to qualify patients for randomization. During the second week, the patient received placebo in a single-blind fashion and recorded in a patient urinary diary (PUD) each void and time of void, each UI episode, and whether the UI episode was associated with urgency for 7 days. The patient proceeded to the treatment period if they had between 7 to 42 urge UI episodes per week at baseline and did not have a total of 3 or more days during the baseline week with no urge UI.

### 3.4 Dose Titration Period

Following the run-in period, patients were randomized equally into one of the two treatment groups: OROS and Ditropan. Randomization was stratified according to the number of U-UI episodes per week at baseline as follows: (1) 7 to 21 (mild urinary incontinence) and (2) greater than 21 (moderate to severe urinary incontinence). The purpose of the dose-titration period, which lasted up to 4 weeks, was to determine at which dose the patient reached the target efficacy endpoint (no U-UI for the last three days of the dosing interval) or if the patient reached the maximum dose of study medication. The patient recorded on the study medication card the date medication was taken. Also, prior to the first dose of medication each morning, the patient recorded on the study medication card their response to the following question:

"Did you have any urinary incontinence associated with urgency during the past 24 hours?"

Ditropan, OROS, and placebo study medications were over-encapsulated for the purpose of blinding and packaged on daily dosing cards. Placebo capsules were identical to those used to over-encapsulate Ditropan and OROS but did not contain oxybutynin. Both the Dose-Titration and Maintenance periods contained active drug and placebo capsules on the cards to maintain blinding and comparable dosing schedules.

Patients began the designated medication at 5 mg/day. During the subsequent one to four clinic visits, in intervals of seven days, dose-escalation occurred in 5 mg/day increments, up to a maximum of 20 mg/day of study medication (OROS or Ditropan). The study medication dose was adjusted according to pre-specified rules. Those patients who reached the target efficacy endpoint or reached the maximum dose of study medication remained at that dose and entered the Maintenance Period.

### 3.5 Maintenance Period

During the one week maintenance period, patients received therapy at dose established during the dose-titration period. Patients received either one to four Ditropan 5 mg capsules per day (5 mg per day to 5 mg four times per day), or one to six OROS 5 mg capsules per day (5 mg/day to 30 mg/day) as a single AM dose. The patient recorded each time they voided, each incontinent episode, and whether the incontinent episode was associated with urgency in a PUD for 7 days. Patients who experienced intolerable anticholinergic effects discontinued study participation.

The patient report of dry mouth was obtained from the patient's report of the adverse event. The investigator solicited adverse events at each assessment time or when otherwise volunteered by the patient. Patients who reported dry mouth were asked by the principal investigator to assess the severity according to the following criteria:

1. *Mild dry mouth*: "Dry mouth relieved with increased fluid or hard candy."

2. *Moderate dry mouth*: "Dry mouth and throat but no difficulty swallowing solid foods (e.g. you can eat a cracker without water)."
3. *Severe dry mouth*: "Very dry mouth and throat, difficulty swallowing solid foods without water (e.g. you could NOT eat a cracker without water)."

New medication cards were distributed and used ones were collected by the investigator at each clinical visit. Patient compliance was monitored by examining the returned used and unused dosage cards during treatment and recording missed doses on the Daily Dosing Record CRF.

## **4.0 STUDY VARIABLES**

### **4.1 Safety Variables**

Safety parameters assessed during the study and recorded on safety CRFs included adverse events, anticholinergic side effects, vital signs, standard laboratory tests.

### **4.2 Primary Endpoint**

The primary parameter was the proportion of patents reporting moderate or severe dry mouth during the maintenance period.

### **4.3 Secondary Endpoints**

Several secondary measurements, which were efficacy related, were assessed using data from the 7 day PUD and patient questionnaires. The first two measurements listed below were key incontinence measurements and were used to demonstrate efficacy of the product. The per protocol secondary measurements were as follow:

1. The reduction in weekly U-UI episodes from baseline to the end of study.
2. The reduction in weekly total UI episodes from baseline to the end of study.
3. The reduction in the number of weekly voids from baseline to the end of the study.
4. The relationship between the level of dry mouth to the level of efficacy achieved.
5. Patient assessment of quality of life as measured by the Urge-Incontinence Impact Questionnaire, a 32 item questionnaire where each item was scored using a six-point scale, which was assessed at the end of the baseline period and at the final visit of the Maintenance period.
6. Patient satisfaction question for treatment received during maintenance period that is scored on a scale of 1 (Not satisfied at all) to 7 (Completely satisfied) which was assessed at the final visit of the Maintenance period.
7. Patient compliance with study medication.

Except for the first measurement, secondary outcome results will not be discussed further in this review as they are considered exploratory by the Medical Officer.

## **5.0 SPONSOR'S STATISTICAL ANALYSIS METHODS**

The following describes the statistical analysis methods as presented by the sponsor in the study report. These methods are per protocol unless otherwise noted.

### **5.1 Analysis Groups and Pooling of Investigators**

All randomized patients were included in the safety analyses. Randomized patients with evaluable baseline and endpoint data were included efficacy analyses. Only patients who

discontinued the study medication prematurely without evaluable endpoint data were excluded from the analysis of efficacy data. The efficacy data from investigational centers with less than two evaluable patients per treatment group were pooled into a single center. Any center with evaluable data from two or more patients in each treatment group were represented separately in the model for efficacy analysis.

## **5.2 Definition of Baseline and Endpoint Measurements**

Baseline measurements were those taken during Week 2 of the run-in period before the dose-titration period. Endpoint was defined as the last available measurement up to the end of study during the double-blind treatment period regardless whether patient was on or off study medication. The last 7 days of available PUD data recorded during the maintenance were used to calculate the primary endpoint. If fewer than seven days were available, then the data were normalized to seven days with the algorithm – Number of episodes = 7 x (Total number of episodes for the period/Number of days of diary information). For baseline and run-in, the same normalization algorithm was used.

## **5.3 Analysis Methods of the Primary Endpoint**

### **5.3.1 Per Protocol Analyses**

All analyses were conducted both on the proportion of subjects with moderate or severe dry mouth, and on the proportion reporting any dry mouth. These proportions were calculated two ways: dry mouth occurring at any point in the randomization phase of the trial and while the patient was on final dose. Data collected from all study centers was pooled to perform the analysis. The Chi Square test was used to analyze the overall results for the differences in proportions of the dry mouth measures.

### **5.3.2 Post-Hoc Analyses**

Survival analysis techniques were used to analyze dry mouth measure. The event was the first report of dry mouth, or moderate or severe dry mouth. These data were analyzed using both time to event and dose to event as a surrogate for time to event. According to the sponsor, dose to event was used as a surrogate for time to event since the dose was adjusted at fixed time intervals, and higher doses are associated with longer total duration of drug exposure (e.g., 5 mg = approximately 2 weeks, 10mg = approximately 3 weeks, 20 mg = approximately 5 weeks).

According to the sponsor, survival analysis techniques were an appropriate method of examining these data because this trial could be viewed as a longitudinal trial with censoring (IND).

This type of analysis would account for each patient's full experience on differing doses.

## **5.4 Analysis Methods of the Efficacy Parameters**

### **5.4.1 Per Protocol Analyses**

A two-way analysis of variance (ANOVA) model or analysis of covariance (ANCOVA) model was used for the analysis of the efficacy parameters: reduction in U-UI and total UI. The ANOVA model was to include treatment, center, and treatment by center interaction factors. The ANCOVA model was to include treatment, center, and treatment by center interaction factors, and baseline number of U-UI episodes per week collected during the Run-in period as

the covariate. The final ANCOVA model was selected from a series of ANCOVA models using the same model selection process as described in PART I, Section 5.3.

The least squares estimate and 95% confidence interval of the mean difference between the two treatment groups in the mean change in the number of weekly U-UI episodes from baseline to the Maintenance Period were calculated. The primary efficacy analysis was the 95% confidence interval of treatment difference, rather than a formal hypothesis test. Both treatments would be considered therapeutically equivalent if the 95% confidence interval of the difference in the mean reduction of U-UI episodes per week was within  $\pm 4$  episodes.

#### *5.4.2 Post Hoc Analyses*

Survival analysis techniques were used to analyze the efficacy measures of U-UI and UI. For U-UI and UI, the event was defined as no incontinence episodes during the one week of maintenance. These data were analyzed using both time to event and dose to event as a surrogate for time to event.

## **6.0 STUDY HYPOTHESIS AND SAMPLE SIZE**

The null hypothesis to be tested was:

*The treatment difference between OROS and Ditropan was equal to zero in the proportion of patients who report moderate to severe dry mouth.*

All statistical tests for treatment comparisons were two-sided and performed at the 0.05 significance level. The sponsor stated that since the primary comparison was the proportion of patients reporting moderate or severe dry mouth, no adjustment of the significance level was done for multiple comparisons.

A sample size of 110 patients for each treatment group was planned. The sponsor claimed that this sample size would provide at least 90% power to detect 20% event rate difference between the two treatment groups at a significance level of 0.05. For this sample size calculation, a moderate to severe dry mouth reporting rate of 15% for OROS was assumed. The assumption was based on the results from a previous study (C-95-049).

The sponsor also claimed that this sample size of 110 patients per group would provide 90% probability to demonstrate therapeutic equivalence based on a one-sided test with significance level of 0.025 assuming a mean reduction of 16 U-UI per week in the Ditropan group and a standard deviation of 9 per week for OROS and Ditropan treatments.

## 7.0 OTHER STUDY INFORMATION

### 7.1 Principal Investigators

Table 7.1 presents the 19 sites that participated in study C-97-020. There were 19 principal investigators and many subinvestigators.

**Table 7.1**  
**Principal Investigators for Study C-97-020**

Principal Investigator	Number of Subinvestigators	Principal Investigator location
Anderson RU	1	Stanford, CA
Antoci J	4	Waterbury, CT
Appell R	2	Cleveland, OH
Blank B	9	Portland, OR
Brito CG	6	Phoenix, AZ
Brown JS	1	San Francisco, CA
Friedlander G	11	Rockville, MD
Gittelman M	10	Aventura, FL
Kaufman JM	0	Aurora, CO
Knoll D	3	Nashville, TN
Mobley D	2	Houston, TX
Munoz D	4	Tacoma, WA
Nair V	1	Monroe, WI
Patton W	6	Tucson, AZ
Saltzstein D	10	San Antonio, TX
Shown T	12	Winston-Salem, NC
Versi E	1	Boston, MA
White C	2	Mobile, AL
Wiatrak M	3	Milwaukee, WI

### 7.2 Patient Enrollment and Randomization

Table 7.2 presents the number of patients enrolled and randomized by each study site. A total of 226 male and female patients were enrolled. These patients were randomized into one of two double-blind treatment groups, 111 patients in the OROS group and 115 in the Ditropan group. Of these 226 patients, 108 (47.8%) were known to be responders prior to screening and 118 (52.2%) were confirmed to be responders during the therapeutic responder screening trial.

**Table 7.2**  
**Number of Patients Enrolled and Randomized by Investigator**

Study Site (Principal Investigator)	Number of Subjects Enrolled (Completed) (N=226)	Randomized to OROS (n=111)	Randomized to Ditropan (n=115)
1 (Anderson)	15 (11)	8	7
2 (Antoci)	7 (4)	4	3
3 (Appell)	1 (0)	0	1
4 (Blank)	4 (4)	2	2
5 (Brito)	12 (11)	6	6
6 (Brown)	20 (20)	10	10
7 (Friedlander)	13 (13)	6	7
8 (Gittelman)	7 (7)	3	4
9 (Kaufman)	12 (12)	6	6
10 (Knoll)	17 (16)	8	9
11 (Mobley)	26 (25)	13	13
12 (Munoz)	13 (13)	7	6
13 (Nair)	3 (2)	1	2
14 (Patton)	22 (21)	10	12
15 (Saltzstein)	20 (20)	10	10
16 (Shown)	4 (4)	2	2
17 (Versi)	4 (24)	2	2
18 (White)	7 (6)	3	4
19 (Wiatrak)	19 (16)	10	9

### 7.3 Patient Accountability and Evaluability

Table 7.3 displays the disposition of the enrolled patients and the number of patients evaluable for the efficacy and safety analyses. This study had very few patients who dropped out [7.5% (17/226)]. Of the 111 patients randomized to OROS, 104 completed the study. Of the 115 patients randomized to oral placebo, 105 completed the study. The dropout rates were similar for both groups: 6.3% (7/111) for OROS and 8.7% (10/115) for Ditropan.

Of the 10 who discontinued study medication prematurely due to adverse event(s), 2 reported dry mouth (Subject \_\_\_\_\_ in Ditropan group). Thus, this study had very few patients who dropped out when they reported dry mouth (2/226= 0.9%).

**Table 7.3  
Patient Accountability**

Disposition	OROS	Ditropan
Number Enrolled in OROS and Oral Placebo Groups	111	115
Number Evaluable for Safety	111	115
Number Completed Study	104	105
Number Who Did Not Complete Study	7	10
Reason for Discontinuation		
Personal Reason*	1	2
Adverse Event**	3	7
Protocol Violation <sup>†</sup>	1	
Lack of Efficacy <sup>‡</sup>	1	1
Lost to Follow-up <sup>§</sup>	1	
Number of Patients Evaluable for Efficacy	104	105
* Patient numbers (OROS) and (Ditropan)		
** Patient numbers (Ditropan) (OROS) and (Ditropan)		
† Patient number (OROS)		
‡ Patient numbers (OROS) and (Ditropan)		
§ Patient number (OROS)		

## 8.0 SPONSOR'S RESULTS

The efficacy results followed by the dry mouth results will be presented. The Division requested that the sponsor had to first demonstrate therapeutic equivalence for the efficacy parameter and then demonstrate that patients treated with OROS experienced less moderate or severe dry mouth than those treated with Ditropan. Only the per protocol analyses results will be presented.

### 8.1 Efficacy Results

The final model for the analysis of the primary efficacy parameter was a two-way ANOVA model with treatment, center, and treatment-by-center interaction factors. Since 5 of the 19 study sites had less than two evaluable patients per treatment group, they were pooled into a single center, as per protocol. These sites had the following Principal Investigators: Antoci, Appell, Friedlander, Nair, and Shown. Eight patients in the OROS group and 10 in the Ditropan group did not enter the maintenance period and were excluded from the analysis of the efficacy parameter.

The results of this analysis are presented in Table 8.1. These results are not from the tables originally cited in the submission. They are based on a reanalysis performed by the sponsor after this reviewer informed them that 12 patients were not used in the ANOVA modeling (Vol. 4.12, Appendix 12.2.7.24, page 33). The sponsor stated in a FAX dated 12-4-98 that:

“As explained, the discrepancy between the numbers of observations cited within the statistical appendixes was due to a minor SAS-related programming error which during that particular pooling of data inadvertently omitted data for investigators whose names exceeded 8 characters. The data from 12 patients of Dr. Gary Friedlander were omitted from the analyses; however, all of the actual data which you currently have are correct.”

The sponsor concluded that "OROS was comparable to Ditropan in reducing the number of weekly U-UI episodes ( $p=0.924$ )."

The sponsor also presented analyses that excluded those patients who had participated in previous OROS trials (C-95-031, C-95-049, and C-96-070). These results are based on the originally submitted tables and may not include the 12 subjects that were missing from the analyses described above and whose results are presented in Table 8.1. The sponsor again concluded that "OROS was comparable to Ditropan in reducing the number of weekly U-UI episodes ( $p=0.838$ ). The 95% confidence interval was (-4.3, 3.5).

**Table 8.1**  
**Efficacy Results**

	No. of U-UI episodes/week
Adjusted mean (SEM) change from baseline:	
OROS (n=103)	-14.9 (1.4)
Ditropan (n=105)	-14.7 (1.4)
Adjusted Mean Difference in Change:	
OROS-Ditropan (SEM)	-0.2 (2.0)
95% Confidence Interval for Difference	(-4.1, 3.7)
OROS vs. Ditropan p-value	0.924

From ANOVA model using OROS and Ditropan groups

## 8.2 Dry Mouth Results

The result for the analysis of the proportion of patients reporting moderate or severe dry mouth at any time after randomization is presented in Table 8.2. There was no significant difference in the reporting of moderate and severe dry mouth during the study between the OROS and Ditropan groups ( $p=0.10$ ).

**Table 8.2**  
**Patients Reporting Moderate or Severe Dry Mouth after Randomization.**  
**All Doses Combined.**

	OROS (n=111)	Ditropan (n=115)	Difference (OROS-Ditropan)	p-value*
Number (proportion) of Patients	19 (0.171)	30 (0.261)	-0.090	0.102

Source: Table 11.1.3.1, Volume 4.6, page 141.

\* Based on two-sample chi-square test.

The result for the analysis of the proportion of patients reporting moderate or severe dry mouth at the final dose for all doses combined is presented in Table 8.3. Again, there was no significant difference in the reporting of moderate and severe dry mouth during the study between the OROS and Ditropan groups ( $p=0.070$ ).

**Table 8.3**  
**Patients Reporting Moderate or Severe Dry Mouth at Final Dose.**  
**All Doses Combined.**

	OROS (n=111)	Ditropan (n=115)	Difference (OROS-Ditropan)	p-value*
Number (proportion) of Patients	18 (0.162)	30 (0.261)	-0.099	0.070

Source: Table 11.1.3.2, Volume 4.6, page 142.

\* Based on two-sample chi-square test.

### 8.3 Safety Results

No death was noted but one serious adverse event occurred in a patient (Subject ) in the Ditropan group during the study treatment period in Study C-97-020 per the Medical Officer. For further safety information, refer to the Medical Reviewer's safety review.

### 9.0 REVIEWER'S COMMENTS ON STUDY DESIGN AND ANALYSES

1. The one week maintenance period in this study did not provide an adequate length of time to demonstrate a realistic efficacy outcome and dry mouth assessment for this chronic use drug. From the Division meeting minutes of the March 11, 1998 teleconference for IND one of the discussion points was that the maintenance period of trial needed to be extended to 6 – 12 weeks in duration. Instead, the maintenance period was 1 week in length. Since incontinence is a chronic condition, the study was not long enough to assess the real clinical outcome of dry mouth from extended treatment use. Thus, care should be taken when interpreting the results of this trial as a longer term result would have provided more realistic information about the performance of each treatment.

2. This is an "enriched" study since only those patients who responded to oxybutynin or other anticholinergic medications were enrolled. This enrichment should be taken into account when interpreting the study results because they are enhanced and cannot be generalized to patients with a diagnosis of urge urinary incontinence.

3. For patients who had less than 7 days of PUD data, the sponsor normalized the weekly PUD measurements to 7 days to derive the baseline and endpoint values by the sponsor. This normalization procedure (Section 5.2) may not reflect the highly variable nature of urge urinary incontinence on a day to day basis.

4. The Division requested an intent-to-treat analysis be conducted for the analysis of the efficacy endpoint of interest. Specifically, the Division meeting minutes of the March 11, 1998 teleconference for IND stated that:

Endpoint measurements should include last observation carried forward.

No ITT analyses were performed by the sponsor or presented in the study report. The sponsor stated in the study report (Volume 4.6, page 113) that:

All randomized patients with evaluable baseline and endpoint data were included in the efficacy analyses. Only the patients who discontinued the study medication prematurely without evaluable endpoint data were excluded from the analysis of efficacy data.

This analysis, which is not an ITT analysis but an efficacy evaluable analysis, was reported in the submission.

5. One principal investigator participated in studies C-95-031, C-95-049, and C-97-020. Six principal investigators participated in studies C-95-049 and C-97-020. One principal investigator participated in studies C-95-031 and C-97-020. The principal investigators and subinvestigators who participated in multiple studies are presented in Table 9.1.

**Table 9.1**  
**Principal Investigators Who Participated in Multiple Studies**

Principal Investigator	Subinvestigators	Study Numbers
Anderson RU	None	C-95-049 C-97-020
Blank B	Kaempf M, Giesy J, Brewer J, Lehman T, McCoy G, Reynolds W, Winchester D, O'Hollaren P, Burke W	C-95-049 C-97-020
Brito CG	Argueso LR, Bailey RB, Bans LL, Bohnert W, Zeidman EJ	C-95-031 C-95-049 C-97-020
Brown JS	None	C-95-049 C-97-020
Kaufman JM	None	C-95-049 C-97-020
Knoll D	Benson R, Minich P	C-95-031 C-97-020
Mobley DF	Woehler T	C-95-049 C-97-020
Saltzstein D	Hundall C, O'Neill T, Terry P	C-95-049 C-97-020

Using the same principal investigators and subinvestigators in more than one Phase 3 clinical trial violates the regulatory requirement of independent studies. Study independence is necessary to demonstrate reproducibility of study results, in this case, therapeutic equivalence. Independence also minimizes bias in study results that may be due to study conduct.

6. Some of the same subjects were used in Studies C-95-031, C-95-049, and C-97-020. One of the exclusion criteria for Study C-97-020 (Volume 4.7, page 47) states that:

Patients who have taken an investigational drug within a period of one month or five times the half-life of the drug (whichever is longer). Patients who have taken oxybutynin chloride as an investigational formulation under ALZA protocols C-95-031, C-95-049 and C-96-070 may be enrolled into this study.

Using the same subjects in more than one Phase 3 clinical trial violates the requirement of independent studies. The potential bias introduced by using the same patients would appear in both the assessment of efficacy (feel that they urinate less than before) and safety (feel less dry mouth) because of familiarity with the intent of the study and use of the treatments. In a telecon with the Division on 12/15/98, the sponsor reported that 3 patients from Study C-95-031 and 13 patients from Study C-95-049 participated in this study (C-97-020), that is 7% (16/226) of patients. Since this reviewer could not find a listing of these 16 subjects in the study report, no formal analyses could be performed. In the opinion of this reviewer, it is anticipated that these 16 patients would not have substantially impacted the results of this study.

7. The sponsor did not present all ANOVA and ANCOVA models evaluated in the analyses of the efficacy measure as was done for studies C-95-031 and C-95-049. Thus, this reviewer could not evaluate how the sponsor selected the final model for the efficacy parameter. The final model was an ANOVA whereas the other two studies resulted in ANCOVA models. Also, the final model selected by the sponsor did not have a statistically significant overall F-value for the ANOVA model and none of the factors were statistically significant.

8. The sponsor did not present efficacy subgroup analyses for gender, age, and race.

9. The protocol was designed to look at dry mouth but in order to get this claim, the Division requested that therapeutic equivalence be demonstrated first before demonstrating the dry mouth claim. Both endpoints are required in order to get the dry mouth claim. Since both comparisons did not reach nominal significance, the dry mouth claim has not been demonstrated.

10. The assessment of dry mouth may not have been adequate because:

- A placebo arm was not included in the study to assess the rate of dry mouth on placebo for comparison to active drug. The Division requested in the meeting minutes of the March 11, 1998 teleconference for IND that a placebo arm should be included in the trial.
- The length of time that the patient was on their maintenance dose of test agent was short, no more than 2 weeks, and did not provide an adequate measure of this outcome. Per the Medical Reviewer, the patient's perception of dry mouth would change the longer they are on medication. The patient may tolerate or become used to the sensation of dry mouth, thus reducing the severity of their dry mouth.
- Dry mouth measurements were not made during the baseline period. In the meeting minutes of the March 11, 1998 teleconference for IND the Division requested that dry mouth measurements should be done during the baseline period and at the end of the trial
- The assessment was made by having the study investigator ask the patient to rate the severity of their dry mouth by giving them several descriptions instead of having the patient fill out a questionnaire independent of the study investigator. The following descriptions were used:  
Mild dry mouth: "Dry mouth relieved with following criteria increased fluid or hard candy."  
Moderate dry mouth: "Dry mouth and throat but no difficulty swallowing solid foods (e.g. you can eat a cracker without water)."  
Severe dry mouth: "Very dry mouth and throat, difficulty swallowing solid foods without water (e.g. you could NOT eat a cracker without water)."  
 This manner of assessing dry mouth may have introduced potential bias in the results due to possible investigator bias in providing the descriptions of dry mouth to the patient.
- Its assessment did not utilize an appropriately validated dry mouth measure. The validation study (Volume 4.9, Section 12.1.8, page 259) conducted gave two self-administered questionnaires, one a visual analog scale and the other a categorical scale as used in the trial, to 40 patients currently taking anticholinergic agents (not necessarily incontinence treatments). The results of this validation study are not applicable to the clinical trial because the clinical trial investigator asked the patient to evaluate the severity of their dry mouth instead of having the patient independently complete a self-administered questionnaire.
- Two other potential sources of bias in the evaluation of dry mouth come from the fact some patients and some study investigators participated in other OROS trials. This lack of independence may result in a familiarity with the study conduct, the treatment, and the possible side effects, which may potentially bias the results.

11. The study did not demonstrate that patients treated with OROS experienced less dry mouth via the per protocol analyses. The difference in the incidence of moderate or severe dry mouth between the two treatments at final dose was not significantly different. The sponsor proposed a 0.20 event rate difference in dry mouth between OROS and Ditropan in the sample size calculation. Instead the event rate difference was 0.099 (0.261 for Ditropan and 0.162 for OROS).

The sponsor then proposed and presented a *post hoc* analysis of the dry mouth data: a Kaplan-Meier survival curve analysis. The Kaplan-Meier survival curve analysis utilized the proportion of patients with moderate or severe dry mouth by dose. For dry mouth, two event types were analyzed. The first event defined was the dose at which the first report of moderate or severe dry mouth occurred, and the second was the dose at which the first report of any dry mouth occurred. But the primary endpoint was the proportion of patients experiencing moderate or severe dry mouth on their final dose, not the dose at which the first report of moderate or severe dry mouth occurred.

The sponsor claimed that dose to event was used as a surrogate for time to event, since the dose was adjusted at fixed time intervals, and higher doses were associated with longer total duration of drug exposure. The assumption of a monotone increasing dose is not valid in this trial. The same dose did not have the same length of time associated with it for all patients. Dose was not strictly related to time as is needed for a survival analysis. Table 9.2 presents the maximum doses that patients reached and the final dose at which they ended the trial.

Some patients dropped to a lower dose after being at a higher dose. For example, in the Ditropan 10 mg/day groups, 47 patients reached a maximum dose of 10 mg/day yet 42 settled at a final dose of 10 mg/day. These 5 patients from the maximum dose of 10 mg/day went to another final dose level.

**Table 9.2**  
**Dose Titration Results: Number (%) of Patients**

Dose (mg/day)	OROS		Ditropan	
	Final Dose	Maximum Dose	Final Dose	Maximum Dose
5	30 (27.0)	29 (26.1)	37 (32.2)	32 (27.8)
10	38 (34.5)	38 (34.2)	42 (36.5)	47 (40.9)
15	22 (19.8)	19 (17.1)	21 (18.3)	20 (17.3)
20	21 (18.9)	25 (22.5)	15 (13.0)	16 (13.9)

Source: Table D, Volume 4.6, page 84.

Thus, since the study did not demonstrate that patients treated with OROS experienced less dry mouth via the per protocol analyses, the sponsor presented *post hoc* analyses that were not appropriate.

## 10.0 STATISTICAL REVIEWER'S ANALYSES AND RESULTS

### 10.1 Efficacy Results

For each patient, the value of the baseline and endpoint number of weekly U-UI episodes were verified to have been calculated using per protocol definition. For baseline, it was the total number of U-UI episodes for the last 7 days on baseline and for maintenance endpoint it was the total number of U-UI episodes for the last 7 days of maintenance.

All but 20 patients had complete baseline data and all but 29 patients had complete maintenance data, i.e., they had data for all 7 days of either the baseline or maintenance period. Of these 20 baseline patients, two had 4 days worth of data, six had 5 days worth of data, and twelve had 6 days worth of data. For the maintenance period, one patient had 2 days worth of data, one had 3 days worth of data, one had 4 days worth of data, two had 5 days worth of data, and twenty-four patients had 6 days worth of data. For these patients, the number of U-UI episodes for each of the missing days was imputed using the following procedure:

Take the sum of the number of U-UI episodes for the available days of data divided by the number of available days of data and round to the closest integer.

This procedure was reasonable to use, per the Medical Officer, since urge urinary incontinence is a highly variable condition on a day to day basis. Preserving the actual number of U-UI episodes for the days where data was available was important in reflecting this variability.

Ninety patients' baseline data value and 24 patients' maintenance data value did not correspond to what the statistical reviewer calculated (See Appendix 1). Of these 114 patients, 10 patients in the baseline period and 3 patients in the maintenance period did not have complete data. All other data values corresponded to what the statistical reviewer calculated.

The statistical reviewer's analysis used the same procedure the sponsor used and described in PART I, Section 5.3. The final two-way ANCOVA model had treatment, center, treatment-by-center interaction factors and baseline weekly U-UI episodes as the covariate. This model differed from the ANOVA model with treatment, center, treatment-by-center interaction factors that the sponsor presented. A two-way ANOVA model with treatment, center, treatment-by-center interaction factors was also fit to the baseline weekly U-UI episode data. Four of the 19 study sites were pooled into a single center, as per protocol. These sites had the following Principal Investigators and differed from the sites pooled by the sponsor: Appell, Blank, Nair, and Shown.

The statistical reviewer conducted a separate analysis of the primary efficacy data using all randomized patients utilizing the last-value-carried-forward ITT technique to account for those patients who did not have maintenance data. This was done because the Division requested this analysis from the sponsor (See Section 9.0, item 6). The results of this analysis are presented in Table 10.1. The result was that OROS was therapeutically equivalent to Ditropan in reducing the number of weekly U-UI episodes from baseline. The 95% confidence interval of (-2.8, 1.5) episodes per week did fall within the *a priori* confidence interval of (-4, 4) episodes per week to demonstrate therapeutic equivalence.

**Table 10.1**  
**Efficacy Results**

	No. of U-UI episodes/week
Adjusted Mean Baseline:	
OROS (n=111)	18.2
Ditropan (n=115)	18.3
Adjusted Mean (SD) Change from Baseline:	
OROS	-13.5 (8.2)
Ditropan	-12.9 (8.2)
Adjusted Mean Difference in Change:	
OROS-Ditropan	-0.6
95% Confidence Interval for Difference	(-2.8, 1.5)
OROS vs Ditropan p-value	0.578

From ANOVA and ANCOVA models using OROS and Ditropan groups.

## 11.0 REVIEWER'S RECOMMENDATION

From a statistical standpoint, the sponsor has provided an adequate and well controlled study that shows evidence for efficacy in support of their intended objective to demonstrate the therapeutic equivalence of OROS to Ditropan in the treatment of urge urinary incontinence as measured by no more than a 4 episode difference in the change from baseline of the weekly number of urge urinary incontinence episodes. But the sponsor has not provided an adequate and well controlled study that shows evidence for the safety measure of dry mouth in support of their intended objective to demonstrate that patients with urge urinary incontinence who are treated with OROS experience less dry mouth compared to Ditropan.

## CONCLUSIONS

There were some problems with the conduct of these trials.

1. The regulatory requirement for independent trials was not preserved because 16 of the 226 patients in Study C-97-020 and 9 of the same study investigators participated in other OROS clinical trials. This lack of independence may result in a familiarity with the study conduct, the treatment, and the possible side effects, which may potentially bias the results.
2. A potential source of bias was in the assessment of the severity of dry mouth. The severity should have been self-assessed by the patient using a questionnaire instead of having the study investigator ask the patient.
3. The length of time that the patient was on their maintenance dose of test agent was no longer than 2 weeks. This was not an appropriate length of time to adequately assess both the efficacy and dry mouth measures for treatment of the chronic condition of urge urinary incontinence.

Although the problems that were encountered in these clinical trials are of concern, the following conclusions may be reached with the information presented:

- OROS was superior to placebo for the treatment of urge urinary incontinence (U-UI), that is, OROS had a significantly larger reduction in the weekly number of episodes of U-UI than placebo did.
- In one of the two therapeutic equivalence studies, OROS was found to be therapeutically equivalent to Ditropan for the treatment of urge urinary incontinence.
- These studies did not demonstrate that patients experienced less dry mouth when using OROS than when using Ditropan.

The numerical results should be interpreted with the caveats that the studies were “enriched” with patients who responded to oxybutynin or other anticholinergic medications, and that the length of the maintenance period was no longer than two weeks.

This reviewer recommends that any new study designed to demonstrate the dry mouth claim should incorporate the following aspects:

- Dry mouth should be measured at baseline.
- A placebo arm would be helpful to assess the rate of dry mouth.
- The length of time that the patient is on their maintenance dose of test agent should be longer than one to two weeks.
- The assessment of the severity of dry mouth should be done by the patient via a self-administered and validated questionnaire.

This reviewer also recommends that all further trials adhere to the regulatory requirement for independent trials; that the length of the maintenance period be longer than 2 weeks; and that intent-to-treat analyses and subgroup analyses for age, gender, and race be reported.

/S/

12/15/98

Sonia Castillo, Ph.D.  
Mathematical Statistician, HFD-715

Concur:

Ed Nevius, Ph.D.  
Division Director

/S/ 12/16/98

/S/

12/15/98

Lisa Kammerman, Ph.D.  
Team Leader

cc:

Archival NDA 20-897

HFD-580/L. Rarick/M. Mann/D. Shames/R. Olmstead/D. Lin/S. Hadar

HFD-715/File Copy/E. Nevius/M. Welch/L. Kammerman/S. Castillo

S. Castillo/x71658/Microsoft Word/12/15/98

This review contains 45 pages of text and tables.



**Study C-97-020: Maintenance**

<b>Patient #</b>	<b>Sponsor</b>	<b>Reviewer</b>
	5	4
	15	13
	8	7
	10	9
	1	0
	25	32
	9	8
	4	3
	3	2
	3	4
	4	3
	28	27
	3	1
	3	2
	5	4
	2	1
	10	11
	21	17
	14	13
	4	3
	4	1
	15	13
	26	28
	18	19