CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-351

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

NDA #: 21-351 (Amendment)

SERIAL #: N000

DRUG NAME: Oxytrol (Oxybutynin) Transdermal System (TDS)

INDICATION: [redacted]

SPONSOR: Watson Laboratories, Inc.

DOCUMENTS REVIEWED:

1. Study report (CDER REC'D Date: August 29, 2002)
2. SAS database in EDR

STATISTICAL REVIEWER: Sue-Jane Wang, Ph.D. (HFD-715)

MEDICAL REVIEWER: Ashok Batra, M.D. (HFD-580)

PROJECT MANAGER: Jean King (HFD-580)

KEY WORDS: Clinical Study, NDA review, LOCF

SWang/301-827-3089/DB2/oxybutynin_nda_2.pdf/02-13-2003

EXECUTIVE SUMMARY

This review pertains to the NDA amendment in response to the March 22, 2002 non-approval action letter. Results from two studies O99009 and O00011 have been submitted. This review has been discussed with the entire review team and the summary of the overall statistical evaluations and comments have been conveyed to the medical review team on Jan. 30, 2003.

STUDY O99009

In this 12-week multi-center (40 sites), randomized, double-blind, placebo-controlled study with a 12-week open-label dose-titration safety period and a 28-week open-label safety extension in patients with urge urinary incontinence, the sponsor withdrew oxybutynin low (1.3 mg/day) and median (2.6 mg/day) dose groups. The main interest in the re-analysis after correction of the data identified during the quality data audit and exclusion of site 12 is the comparison between oxybutynin high dose (3.9 mg/day) vs. placebo.

This reviewer confirmed the sponsor's results, which considered a mITT cohort of treatment actually received. The sponsor pre-specified the RT-2 rank procedure in place of ancova when the normality assumption fails. This reviewer analyzed the electronic data set and performed analyses based on as randomized mITT cohort and common rank procedure. The statistical significance for all three important efficacy outcomes, number of urinary incontinence episodes per week, average daily urinary frequency, and average daily urinary volume per void, was still observed.

STUDY O00011

This study was a multi-center (48 sites), randomized, double-blind, double-dummy, placebo-controlled study comparing oxybutynin transdermal system (TDS) versus active-controlled tolterodine long acting capsules in patients with overactive bladder (OAB) who have achieved a beneficial response on their current anticholinergic treatment. Eligible patients during the screening and baseline evaluation were to be randomized to receive either 3.9 cm^2 oxybutynin TDS (+ placebo capsules), 4 mg tolterodine long acting capsules (+ placebo TDS) or placebo (capsules and TDS) treatment. Statistical significance was observed based on the protocol pre-specified primary efficacy outcome, change from baseline in the number of urinary incontinence episodes per day (p=0.0137). However, as stated in the non-approval letter, the medical review team considers demonstration of efficacy for average urinary frequency clinically important for establishing efficacy in the treatment of patients with OAB.

Oxybutynin TDS 3.9 mg/day (or 39 cm^2) administered in a twice-weekly regimen was shown to be effective compared to placebo during chronic treatment in patients with OAB in one placebo-controlled double-blind Phase III trial (Study O99009). The median improvement in the 39 cm^2 oxybutynin treated group was less than one episode less per day (or 0.57 episodes per day) or equivalently, 4 episodes reduction per 7 days as compared with placebo. Such improvement was 1 episode reduction per 3 days (or 0.33 episodes per day) as compared with placebo in Study O00011. Based on the pre-specified primary efficacy outcome, oxybutynin TDS was shown statistically effective when compared to placebo in the reduction of number of urinary incontinence episodes per week. There were no consistent statistical evidences among the results of the sensitivity analyses performed in the secondary efficacy outcomes of change in average daily urinary frequency, however, consistent evidence was observed in the average urinary volume per void in both studies.

1 BACKGROUND

Oxybutynin is currently available in the United States for oral administration as immediate-release tablets, syrup, and a recently introduced once-daily controlled-release form (Ditropan-XL®) to treat patients with overactive bladder (OAB). Oral administration of oxybutynin is known to be associated with anticholinergic side-effects such as xerostomia (dry mouth), blurred vision, nausea, loss of appetite, constipation, urinary retention, drowsiness, dizziness, depression and abdominal pain (Moore et al., 1990, Tapp et al., 1990).

Watson Laboratories, Inc. (the sponsor) has developed a transdermal system for the delivery of oxybutynin (Oxybutynin TDS). TDS requires less frequent dosing, which is believed to increase the potential for improved patient compliance. The sponsor has submitted a phase II study (O096017) in which TDS oxybutyin treatment efficacy on urge urinary incontinence (UI) was compared with oral form and a phase III study (O099009) in which TDS oxybutynin treatment efficacy on improvement of number of UI per week was compared with placebo. This was the content of the original NDA submission.

The Agency issued a non-approval letter dated March 26, 2002 after the review of the original NDA filed on April 26, 2001. One of the deficiencies related to the [redacted]. In response to this non-approval letter, the sponsor submitted this amendment to the original NDA intended to address the remaining three action items identified in the Agency's non-approval letter. These items are:

(1) Address the "marginal efficacy" shown in the single phase III clinical trial that was in the NDA (study O99009), including the fact that it did not demonstrate a significant reduction in urinary frequency, a secondary endpoint that FDA described as "clinically important" in establishing efficacy for treatment of OAB;
(2) Provide a reanalysis of the data in the O99009 study to account for certain diary transcription errors, and
(3) Provide additional data on skin irritation for OXYTROL 3.9 mg/day.

According to the sponsor, the Agency has agreed that the sponsor would submit (1) reanalysis of Study O99009 which includes a number of corrections to the database due to the results obtained from the data quality audit, and (2) a new study of OXYTROL (Study O00011), a 21-day cumulative irritation study of OXYTROL 3.9 mg/day in response to the action letter.

This review pertains to the sponsor's submission of reanalysis of Study O99009 and the efficacy evaluation of Study O00011.

2 STUDY OVERVIEW

2.1 STUDY O99009

2.1.1 TRIAL DESCRIPTION

This was a 12-week multi-center (40 study sites), randomized, double-blind, placebo-controlled study with a 12-week open-label, dose-titration, safety period and a 28-week open-label safety extension in patients with urge urinary incontinence. Patients who met the eligibility criteria during the screening and baseline evaluations were randomized to one of the following treatment groups: 13 cm^2 Oxybutynin TDS, 26 cm^2 Oxybutynin TDS, 39 cm^2 Oxybutynin TDS, or placebo TDS.

The primary objective was to compare the safety and efficacy of 3 doses of oxybutynin TDS with placebo during 12 weeks of treatment and the secondary objective was to compare the daily urinary frequency, urinary volume per void, quality of life (QoL) scores, global assessment of disease state, as well as safety assessments. The primary efficacy endpoint was "the change from baseline to endpoint in the double-blind period in the number of urinary incontinent episodes per week recorded in the 7-day urinary diary by patients receiving active treatment versus those receiving placebo."

Patients who completed the double-blind period were eligible to enter the 12-week, open-label, dose-titration safety period. In the open-label safety period, all patients began treatment with a single 13 cm^2 oxybutynin TDS applied twice weekly. The dose of medication was titrated by the investigator after 2 and 4 weeks of treatment based on patients' symptoms and remained fixed for the last 8 weeks. For the open-label safety period, change from baseline to endpoint (week 24, visit 10 or LOCF) for the primary measurement was analyzed by final dose group. Characterization of the distribution of doses used by the patients in the study, confirmation of continued efficacy using both objective and subjective measures, and continued treatment safety in approximately 300 patients, changes in QoL scores over the 12-week open-label safety period, plasma concentrations of oxybutynin and its primary active metabolite were also of interest.

Patients who completed the 12-week open-label safety period had the option to continue into a 28-week, open-label, fixed-dose safety extension. Participation was limited to approximately 150 patients from the top-performing sites in order to ensure exposure in 100 patients. The results of the 28-week open-label safety extension were reported separately. **This review focuses on the reanalysis of the study.**

URINARY DIARY

A 7-day urinary diary was used to record the time of normal voids, times of urinary incontinence, estimated amount of leakage, and etiology of incontinence episode (urge or stress). In addition, on two consecutive days during each diary period (a 48-hour period of the patient's choosing), patients were required to collect all urine during normal voids and record the voided volume. Patients must be individually trained on the use of the urinary diary and must practice recording urine volume during the baseline evaluation (Visit 2). Patients were required to visit the clinic upon completion of Weeks 3, 6, 9, and 12 (Visits 4 through 7) of the double-blind period of the study.

2.1.2 THE SPONSOR RESULTS OF THE REANALYSIS AND REVIEWER'S COMMENTS

PATIENT DISPOSITION

Five hundred and twenty patients were enrolled and randomized at 40 sites: 132 (25.4%) to receive placebo, 130 (25%) 13 cm^2 oxybutynin TDS, 133 (25.6%) 26 cm^2 oxybutynin TDS, and 125 (24%) 39 cm^2 oxybutynin TDS. Four hundred forty-seven (86.0%) of the 520 treated patients completed the double-blind period. A total of 73 (14.0%) patients discontinued prematurely from the double-blind study. Details of the original NDA review can be found in the DFS system.

RE-ANALYSIS OF EFFICACY ENDPOINTS

The primary efficacy analysis was to compare the change in number of urinary incontinence episodes from baseline to end of the double blind period (Week 12, Visit 7) using last observation carried forward (LOCF) imputation for patients not completing the double-blind period. The number of episodes was obtained from the 7-day urinary diary and was normalized to seven days for patients with less than seven days of recorded data.

Secondary efficacy analyses was to compare the mean change in average daily urinary frequency and the mean change in average urinary volume per void from baseline to the end of the double-blind period using LOCF imputation for patients not completing the double-blind period. Average daily urinary frequency was calculated by dividing the total number of events recorded on the 7-day urinary diary by the total number of days with data recorded in the diary. Average urinary volume per void was calculated by dividing the sum of the voided volumes by the total number of voids recorded during the 2-day urine volume documentation.

The original statistical analysis plan was applied to the reanalysis of the revised data in this submission. That is, the above efficacy parameters were analyzed using an analysis of covariance (ANCOVA) with the

average daily baseline measure of that efficacy parameter as the covariate and effects of treatment and center. The RT2 transformation was employed if the normality assumption was violated. Hypothesis tests for each of the three active treatment effects compared to placebo were conducted using differences of adjusted means. To control the maximum experiment Type I error at α=0.05, the comparisons were made using Dunnett's method.

- **PRIMARY EFFICACY: Change in Number of Urinary Incontinence Episodes per Week**

During the double-blind period, patients in the mITT cohort treated with the 39 cm^2 TDS experienced a statistically significant decrease in the number of urinary incontinence episodes per week from baseline to endpoint (p = 0.0165) compared with placebo. The median number of incontinence episodes in the 39 cm^2 group decreased by 19 (61.3%) episodes per week compared with the median decrease of 14.5 episodes per week in the placebo group. No significant differences from placebo were found for the 13 cm^2 or 26 cm^2 groups (a median decrease of 14.0 episodes per week in the 13 cm^2 group and 15.0 in the 26 cm^2 group).

Table 11.4-1: Summary of number of urinary incontinence episodes per week at baseline and change from baseline to endpoint – double-blind period (mITT cohort omitting Site 12) – Study O99009

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 127		n = 127		n = 128		n = 120	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Number of urinary incontinence episodes per week								
Baseline (Visit 3)								
Mean and SD	37.7	24.0	38.2	26.5	35.8	22.5	34.3	18.2
Median	30.0		31.0		30.0		31.0	
Endpoint change from baseline								
Mean and SD	-19.2	21.4	-18.2	19.7	-16.8	17.9	-21.0	17.1
Median	-15.0		-15.5		-14.0		-19.0	
P-value[1]			0.9927		1.0000		0.0265	

[1]Active treatment vs. placebo. P-value derived from Dunnett's test. Comparison significant if $p \leq 0.05$

Source: Table 14.2.1.1.5.1; Listing 16.2.7.1.1

Site 12 was excluded from the re-analysis as a result of scientific data audit in the original submission. There were 4 patients in placebo, 3 in 13 cm^2 oxybutynin TDS, 3 in 26 cm^2 oxybutynin TDS, and 4 in 39 cm^2 oxybutynin TDS groups in site 12. The patient numbers from the above Table excluded site 12. The sponsor has conducted a reanalysis based upon the data quality audit that resulted in a number of corrections to the database. Primarily these involved several missing diary pages that had been inadvertently omitted from the database that was originally analyzed but were later located at the clinical sites as a result of the audit.

According to the sponsor, by excluding site 12 and including the additional diary information from the audit, results of the three important efficacy endpoints measured as change from baseline to endpoint at double-blind phase: (1) urinary incontinence episodes per week, (2) average daily urinary frequency, and (3) average urinary volume per void, are summarized in the sponsor Table 11.4-1, Table 11.4-3, and Table 11.4-5, respectively.

The review team initially had concerns about 31 patients with missing/incomplete diary data and 4 patients with wrong baseline data. This reviewer had faxed the sponsor on January 31, 2003 and requested the sponsor to address the following two questions: (1) Did the reports in Tables 11.4-1, 11.4-3, and 11.4-5 include corrected data f the 31 patients with incomplete diary data? Please provide a listing containing patient ID#, treatment arm, and their names, and (2) Regarding the four patients with 'wrong' baseline

diaries, what study arms were they from and were these four patients included in the analysis? What are their ID#? Were they from site 12?

In response to the two questions stated above, the sponsor indicated that the changes in the derived efficacy parameter values resulting from the diary corrections in the database were submitted in the final study report and could be located in the Special Listings 16.2.7.1.1 and 16.2.7.1.2 of volume 113. Due to the inconsistent numbering system, the sponsor further submitted these two listings as a review aid on February 07, 2003.

Table 11.4-3: Summary of average daily urinary frequency and change from baseline to endpoint – double-blind period (mITT cohort omitting Site 12) – Study O99009

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 127		n = 127		n = 128		n = 120	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Daily urinary frequency (episodes)								
Baseline (Visit 3)								
Mean and SD	12.3	3.5	12.5	3.7	11.8	2.8	11.8	3.1
Median	11.0		11.0		11.0		11.0	
Endpoint change from baseline								
Mean and SD	-1.6	3.0	-1.9	2.6	-1.8	2.4	-2.2	2.5
Median	-1.0		-2.0		-2.0		-2.0	
P-value[1]			0.6805		0.3510		0.0313	

[1]Active treatment vs placebo. P-value derived from Dunnett's test. Comparison significant if $p \leq 0.05$.

Source: Table 14.2.1.1.5.2; Listing 16.2.7.1.1

Table 11.4-5: Summary of average urinary volume per void at baseline and change from baseline to endpoint – double-blind period (mITT cohort omitting Site 12) – Study O99009

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 127		n = 127		n = 128		n = 120	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Average urinary volume per void (mL)								
Baseline (Visit 3)								
Mean and SD	175.9	69.5	164.8	68.8	155.7	63.0	171.6	65.1
Median	166.5		162.0		145.5		168.0	
Endpoint change from baseline								
Mean and SD	10.5	56.9	8.6	68.0	25.1	58.3	31.6	65.6
Median	5.5		6.0		19.0		26.0	
P-value[1]			0.9432		0.0063		0.0009*	

[1]Comparison significant if $p \leq 0.0167$

* Comparison for 39 cm^2 at endpoint significant for the 25 percentile value of the covariate ($p = 0.0001$) and the median ($p = 0.0005$) only using the unequal slopes model.

Source: Table 14.2.1.1.5.3; Listing 16.2.7.1.1; Appendix 16.1.9.2.1.5.3, p. 149

2.1.3 REVIEWER'S EVALUATION AND COMMENTS

Regarding the reanalysis of this study, assuming that there were no transcription errors in correcting the incorrect or missing diary data, the sponsor's reanalysis included 10 patients from placebo, 5 patients from 13 cm^2 oxybutynin arm, 12 patients from 26 cm^2 oxybutynin arm, and 6 patients from 39 cm^2 oxtybutynin

arm, who had at least one of the three efficacy measurements 'corrected' during the double blind phase of the trial. According to the sponsor, none of the patients with baseline diary errors were from Site 12.

Note that the sponsor pre-specified the RT-2 rank procedure when the normality assumption fails. This reviewer confirmed the above results reported by the sponsor, viz., exclusion of patients from Site 12 and correction of missing/incomplete diary data or wrong baseline data. It is noted that the mITT cohort was defined as all patients who received at least one application of a TDS and provided data for at least one efficacy assessment after the first application. There were 6 patients with wrong treatment assignment during treatment randomization of the double-blind period. The treatment assignment used for analysis using the mITT cohort was the treatment actually received. This reviewer analyzed the electronic data set in this amendment NDA submission. Additional analyses include use of "as randomized" mITT cohort, use of the common rank procedure on the change from baseline using either the original ancova model or a model excluding the pooled center term. Statistical significance for all three outcomes was still observed for the 39 cm^2 oxybutynin patch.

2.2 STUDY O00011

2.2.1 TRIAL DESIGN SYNOPSIS

This study was a multi-center (48 sites), randomized, double-blind, double-dummy, placebo-controlled study comparing oxybutynin TDS versus active-controlled tolterodine long acting capsules in patients with overactive bladder (OAB) who have achieved a beneficial response on their current anticholinergic treatment. Eligible patients during the screening and baseline evaluation were to be randomized to receive either 39 cm^2 oxybutynin TDS (+ placebo capsules), 4 mg tolterodine long acting capsules (+ placebo TDS) or placebo (capsules and TDS) treatment. Transdermal systems were applied twice weekly to the abdomen, and a capsule was taken once daily, for the 12-week randomized, double-blind, double-dummy, treatment period. The screening period consisted of a 2-week washout from current OAB treatment, practice of bladder and fluid management techniques, and completion of a 3-day urinary diary at the end of the 2-week period. The 3-day urinary diary collection was to be performed at week-2, week-6, and week-12 during the treatment period.

The primary efficacy endpoint was the change from baseline (visit 3) to the end of treatment (visit 6, week-12) in the number of incontinent episodes recorded on the 3-day urinary diary. The supportive efficacy endpoints included change in average daily urinary frequency and change in average urinary volume per void from the baseline to the end of the double-blind treatment period, etc. In the protocol, the sponsor stated that all inference tests will be conducted at $\alpha = 0.05$ (two-sided) on the null hypothesis of no difference between the treatment groups. The statistical analysis method specified in the protocol was the same as protocol O99009 study, viz., ancova model adjusting for baseline covariate and the pooled center.

Reviewer's comments: The statistical analysis plan (SAP) was finalized on Dec. 10, 2001. The initial plan, approved on May 29, 2001 was amended 3 times prior to database lock and study unblinding. Mainly, these amendments were (1) identified the mITT cohort as the primary analysis population, (2) added the mITT cohort to the definition list, (3) added an analysis plan for the equivalence test of TDS oxybytunin vs. oral tolterodine if the distributional assumptions of the analysis were not met. The mITT included all patients who received at least one dose of study medication and had data for at least one efficacy assessment after the first dose (visit 3). For the item (3), the amendment was 'in the event that the normality assumptions for the ancova do not hold as described in the Appendix C.1, the 95% confidence intervals analyzing equivalence between transdermal oxybutynin and oral tolterodine will be calculated for the difference in medians.'

Sample size estimation was based on the primary efficacy endpoint. It was assumed that a common standard deviation was 3.1 episodes per day. A difference between TDS oxybutynin and placebo of 1.5 episodes per day could be detected with 87% power with 100 patients in each group. The sponsor stated that such sample size would have more than 90% power to show equivalence (two-sided 95% confidence

intervals) between TDS oxybutynin and oral tolterodine with respect to reduction from baseline in number of incontinence episodes.

2.2.2 *THE SPONSOR RESULTS AND REVIEWER'S COMMENTS*

PATIENT DISPOSITION

The trial was started on April 23, 2001 and completed on Oct. 12, 2001 for the double-blind phase. A total of 361 patients were enrolled and randomized to receive 3.9 mg/day oxybutynin TDS (n=121, 33.5%), placebo (117, 32.4%) and 4mg tolterodine long-acting capsules (123, 34.1%). Early discontinuation rate in oxybutynin TDS treated patient (19.8%) was more than twice than placebo (8.5%) patients and was more than threefold than the tolterodine (5.7%) treated patients. The apparent excess of withdrawal rate in oxybutynin TDS group was primarily due to adverse events.

	Placebo (n=117)	Oxybutynin TDS (n=121)	Tolterodine capsule (n=123)
Completed	107	97	116
Withdrawn	10 (8.5%)	24 (19.8%)	7 (5.7%)
w d due to AEs	3 (2.6%)	16 (13.2%)	4 (3.3%)
due to loss to followup	1 (0.9%)	2 (1.7%)	1 (0.8%)
due to patient decision	6 (5.2%)	6 (5.0%)	2 (1.6%)

Patients were primarily Caucasian women with a lengthy history of OAB. Patients' age ranged from 18 to 89 years with an average age of 63 years. The median duration of pharmacological treatment for OAB was approximately 1 year.

EVALUATION OF IMPORTANT EFFICACY OUTCOMES

- **PRIMARY EFFICACY: Change in Number of Urinary Incontinence Episodes per Day**

The sponsor's report on the change in number of urinary incontinence episodes per week is summarized in the sponsor's Table 11.4-1 (p.55 of vol.2.269). In addition, the other two important secondary efficacy outcomes, change in average daily urinary frequency (the sponsor Table 11.4-3), and change in average urinary volume per void (the sponsor Table 11.4-4) are also summarized below.

Table 11.4-1: Daily urinary incontinence episodes at baseline and change from baseline to endpoint (Study O00011)

	Placebo	Tolterodine	Oxybutynin TDS
	n = 117	n = 123	n = 121
Number of urinary incontinence episodes per day at baseline (Visit 3)			
Mean (SD)	5.0 (3.2)	5.0 (2.9)	4.7 (2.9)
Median	4.0	4.0	4.0
Change from baseline in number of urinary incontinence episodes per day (endpoint)			
Mean (SD)	-2.1 (3.0)	-3.2 (2.8)	-2.9 (3.0)
Median	-2.0	-3.0	-3.0
P-value versus placebo comparing least squares adjusted means		0.0011	0.0137
95% CI for the difference between Tolterodine and Oxybutynin TDS for median change from baseline			(-1.0, 0.0)

Source: Table 14.2.1.1.2; Listing 16.2.7.1.2; Double-blind period, mITT cohort

As shown in Table 11.4-1, oxybutyin TDS treatment appeared to be significantly superior to placebo in reducing the number of daily urinary incontinence episodes (p=0.0137). Treatment with tolterodine also

showed a significant decrease of 3 incontinence episodes per day (p=0.0011) over placebo. The sponsor claimed that oxybutynin TDS and tolterodine were comparably effective (95% CI was –1.0 to 0.0).

Table 11.4-3: Urinary frequency and change from baseline to endpoint (Study O00011)

	Placebo	Tolterodine	Oxybutynin TDS
	n = 117	n = 123	n = 121
Number of micturitions per day at baseline (Visit 3)			
Mean (SD)	12.3 (3.3)	12.1 (3.3)	12.4 (2.9)
Median	12.0	12.0	12.0
Change in baseline in number of micturitinos per day (endpoint)			
Mean (SD)	-1.4 (2.7)	-2.2 (2.6)	-1.9 (2.7)
Median	-1.0	-2.0	-2.0
P-value versus placebo comparing least squares adjusted means		0.0025	0.1010

Source: Table 14.2.1.2.2; Listing 16.2.7.1.2; Double-blind period, mITT cohort

Table 11.4-4: Urinary volume per void at baseline and change from baseline to endpoint (Study O00011)

	Placebo	Tolterodine	Oxybutynin TDS
	n = 117	n = 123	n = 121
Average urinary volume per void (mL) at baseline (Visit 3)			
Mean (SD)	175.0 (68.0)	165.2 (61.1)	164.8 (62.3)
Median	171.0	150.0	160.0
Change from baseline in average urinary volume per void (endpoint)			
Mean (SD)	9.3 (63.1)	29.3 (56.9)	32.0 (55.2)
Median	5.5	29.0	24.0
P-value versus placebo comparing least squares adjusted means		0.0017	0.0010

Source: Table 14.2.1.3.2; Listing 16.2.7.1.2; Double-blind period, mITT cohort

However, oxybutynin TDS treatment was not shown to be significantly superior to placebo in reducing the number of urinary frequency (p=0.1010), as shown in the sponsor Table 11.4-3, although a significant reduction in the average urinary volume per void (p=0.001) was observed, see the sponsor Table 11.4-4. In contrast, tolterodine treatment appeared to be superior to placebo in reducing the number of urinary frequency (p=0.0025), see the sponsor Table 11.4-3 and in reducing the average urinary volume per void (p=0.0017), as shown in the sponsor Table 11.4-4.

2.2.3 REVIEWER'S EVALUATION AND COMMENTS

This reviewer analyzed the electronic data and obtained the summary statistics very similar to the sponsor's summary results on the mean (SD), median for the baseline measurements and the change from baseline to the endpoint, with minor differences in significant digits. This reviewer performed additional analyses using the usual rank procedure to investigate the robustness of the RT-2 rank transformation performed by the sponsor. This reviewer also performed the analyses based on as randomized mITT cohort. The results in terms of statistical significance are consistent with the sponsor's finding. That is, in comparison to the placebo, there is generally consistent statistical evidence of oxybutynin TDS effect and tolterodine effect on the primary efficacy outcome (change in average number of urinary incontinence episodes per day) and a secondary efficacy outcome of change in average urinary volume per void. However, oxybutynin TDS failed to show a statistically significant improvement over placebo on change in average daily urinary frequency, an efficacy outcome the medical division considers clinically important for establishing efficacy

in the treatment of patients with OAB. It is noted that this latter secondary efficacy endpoint was not the primary efficacy endpoint pre-specified in the original analysis plan.

Interpreting the active comparator results

Although the sponsor claimed that oxybutynin TDS and tolterodine were comparably effective (95% CI for the difference between tolterodine and oxybutynin TDS for median change from baseline was –1.0 to 0.0), it is noted that the study was not designed to study the equivalence between tolterodine versus oxybutynin TDS. In addition, there was no pre-specified equivalence margin to objectively judge the evidence of statistical equivalence. To weigh the risk benefit between the oxybutynin TDS treatment and the active tolterodine from the result in this study, this reviewer would like to point out the following points:

- The early discontinuation rate was more than twofold with oxybutynin TDS (19.8%) when compared to either the placebo arm (8.5%) or the active tolterodine capsule arm (5.7%). The differences were primarily attributed to a four-fold increased rate of 'AE withdrawal' with oxybutynin TDS (13.2%) as compared to the tolterodine capsule treatment (3.3%), which is similar to that of placebo arm (2.6%);
- If both the number of urinary incontinence episodes per day and the micturition frequency per day are clinically important efficacy endpoints, a possible evaluation of statistical equivalence between oxybutynin TDS and the tolteroidine would require that evidence of equivalence be shown for both efficacy outcomes. The premise, however, would require that each treatment be shown to be superior to placebo. The above criteria might be reasonable for the efficacy endpoint of "number of urinary incontinence episodes per day" if no pre-specification of the equivalence margin can be accepted. Clearly, the same argument cannot be applied for the urinary frequency per day efficacy endpoint since the oxybutynin TDS effect was not shown to be superior to placebo (p=0.1010) whereas the active tolterodine effect was observed (p=0.0025).

3 SUMMARY

In this amendment to the original non-approval NDA, the sponsor submitted (1) results of the reanalysis of the original Study O99009 after data correction and exclusion of Site 12, and (2) results of a new trial O00011 for review seeking approval of oxybutynin TDS 3.9 mg/day dosing. The statistical review and evaluation of the reanalysis of Study O99009 assumed that there were no transcription errors in correcting the incorrect or missing diary data and the exclusion of patients from Site 12.

Statistical significance was observed based on the protocol pre-specified primary efficacy outcome, change from baseline in the number of urinary incontinence episodes per week in Study O99009 re-analysis (p=0.0265) and in Study O00011 (p=0.0137), see Table 3.8-1 in vol. 1, p.79 and summarized below.

Table 3.8-1: Number of urinary incontinence episodes per week (O99009) or daily (O00011) at baseline and change from baseline to endpoint (O99009 mITT omitting Site 12, O00011 mITT)

	O99009		O00011	
	Placebo	Oxytrol 3.9 mg/day	Placebo	Oxytrol 3.9 mg/day
	n = 127	N=120	N=117	n = 121
Baseline (Visit 3)				
Mean (SD)	37.7 (24.0)	34.3 (18.2)	5.0 (3.2)	4.7 (2.9)
Median	30.0	31.0	4.0	4.0
Endpoint change from baseline				
Mean (SD)	-19.2 (21.4)	-21.0 (17.1)	-2.1 (3.0)	-2.9 (3.0)
Median	-15.0	-19.0	-2.0	-3.0
P-value[1]		0.0265*		0.0137*

* comparison significant if $p < 0.05$

Source: O99009 Table 14.2.1.1.5.1; Listing 16.2.7.1.1; Source: O00011 Table 14.2.1.1.2; Listing 16.2.7.1.2

If the approval standard is to be based on the medical division's modified criteria stated in the Agency's non-approval letter to the sponsor, viz., demonstration of efficacy on the average daily urinary frequency, then, there is one positive result (p=0.0313 in Study O99009) and one negative result (p=0.1010 in Study O00011), see Table 3.8-3.

Table 3.8-3: Average daily urinary frequency and change from baseline to endpoint (O99009 mITT omitting Site 12, O00011 mITT)

	O99009		O00011	
	Placebo	Oxytrol 3.9 mg/day	Placebo	Oxytrol 3.9 mg/day
	n = 127	N=120	N=117	n = 121
Baseline (Visit 3)				
Mean (SD)	12.3 (3.5)	11.8 (3.1)	12.3 (3.3)	12.4 (2.9)
Median	11.0	11.0	12.0	12.0
Endpoint change from baseline				
Mean (SD)	-1.6 (3.0	-2.2 (2.5)	-1.4 (2.7)	-1.9 (2.7)
Median	-1.0	-2.0	-1.0	-2.0
P-value[1]		0.0313		0.1010

Source: O99009 Table 14.2.1.1.5.2; Listing 16.2.7.1.1; Source: O00011 Table 14.2.1.2.2; Listing 16.2.7.1.2

4 CONCLUSION

Oxybutynin TDS administered in the dosage strength of 39 cm^2, in a twice-weekly regimen was shown to be effective compared to placebo during chronic treatment in patients with overactive bladder in one placebo-controlled double-blind Phase III trial (Study O99009). The median improvement in the 39 cm^2 Oxybutynin treated group was less than one episode reduction per day (or 0.57 episodes per day) or equivalently, 4 episodes reduction per 7 days compared with placebo. Such improvement was 1 episode less per day as compared with placebo in Study O00011. Based on the pre-specified primary efficacy outcome, oxybutynin TDS was shown to be statistically effective when compared to placebo in reduction of number of urinary incontinence episodes per week or per day. The observed significant effect was supported by a numerical improvement of change in average daily urinary frequency and a statistically significant improvement of change in average urinary volume per void.

References

Moore KH, Hay DM, Imrie AE, Watson A, Goldstein M (1990). Oxybutynin hydrocholoride (3 mg) in the treatment of women with idiopathic detrusor instability. Br J Urol 66:479-85.

Tapp AJS, Cardozo LD, Versi E, Cooper D (1990). The treatment of detrusor instability in postmenopausal women with oxybutynin chloride: a double-blind placebo controlled study. Br J Obstet Gynaecol 97:521-6.

Sue-Jane Wang, Ph.D.
Senior Mathematical Statistician

Concur: S. Edward Nevius, Ph.D.
Division Director, HFD-715

Mike Welch, Ph.D.
Statistical Team Leader of HFD-580

cc:
Archival NDA# 21-351
HFD-580/Shame, Hirsch, Batra, King
HFD-715/Anello, Nevius, Welch, Wang

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sue Jane Wang
2/13/03 01:48:22 PM
BIOMETRICS

Mike Welch
2/13/03 01:52:16 PM
BIOMETRICS
Concur with review

S. Edward Nevius
2/13/03 04:13:44 PM
BIOMETRICS
Concur with review.

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-351
Applicant:	Watson Laboratories, Inc.
Name of Drug:	Oxybutynin transdermal system (TDS)
Indication:	
Documents Reviewed:	Vol.1.1, Vol.1.28, 1.45, 1.134, 1.140-143, 1.154, 1.158, 1.163, and 1.247 and SAS Database dated August 14, 2001 and August 30, 2001
Medical Officer:	Brenda Gierhart, M.D. (HFD-580)
Statistical Reviewer	Sue-Jane Wang, Ph.D. (HFD-715)

This review has been discussed with the entire review team.

EXECUTIVE SUMMARY

STUDY O99009

The sponsor changed the study conduct to include the extended open-label safety study. In addition, the sponsor changed the planned analyses of parametric ANCOVA to non-parametric ranking procedure.

This reviewer confirmed "the distributional normality assumption of the parametric ANCOVA failed to hold for parameters based upon the diary data (change in number of urinary incontinence episodes per week, change in average daily urinary frequency, change in average urinary volume per void)." This reviewer performed a few analyses to investigate the robustness of the treatment effect of 39 cm^2 Oxybutynin relative to placebo based on "the change from baseline of the number of UI episodes per week", the primary efficacy endpoint. At the baseline, the median number of urinary incontinence episode per week was 30 to 31 among the four groups. In the 12-week double-blinded phase, placebo treated patients showed an improvement of 14.5 episodes less per week. In contrast, 15.0, 14.0, and 19.0 episodes less per week were observed in the 13 cm^2, 26 cm^2 and 39 cm^2 groups, respectively. The results showed a marginal statistical significance of the 39 cm^2 Oxybutynin group: the median improvement was less than one episode per day (or 0.64 episodes per day) equivalently, 4.5 episodes per 7 days. There was no consistent statistical evidence among the results of the sensitivity analyses performed in the secondary efficacy outcomes of change in average daily urinary frequency and average urinary volume per void. In addition, there was no statistically significant finding with the global assessment of disease state. It is noted that there is only one phase III study in this submission.

STUDY O96017

In this phase II, double-blind, active controlled trial, the difference in responder rates between the TDS Oxybutynin and the oral Oxybutynin was –2% with 95% CI of –17% to 13%, the lower limit of the 95% CI clearly fell outside the equivalence margin of 15%. By the protocol definition, the study failed on the primary efficacy outcome, the responder rate, based on the evaluable patients. The sponsor also reported the results based on the ITT patients. The difference in responder rates (TDS – oral) was –5% with 95% CI of –20% to 10%. The lower limit of the 95% CI was worse with the ITT analysis (-20%) than the evaluable analysis (-17%). Hence, from the pre-specified statistical criteria, the study failed to conclude that responder rate in TDS Oxybutynin treated group is equivalent to the oral Oxybutynin treated group.

Key Words: Clinical Study, NDA Review

TABLE OF CONTENTS

1 BACKGROUND

Oxybutynin is currently available in the United States for oral administration as immediate-release tablets, syrup, and a recently introduced once-daily controlled-release form (Ditropan-XL®) to treat patients with overactive bladder. Oral administration of oxybutynin is known to be associated with anticholinergic side-effects such as xerostomia (dry mouth), blurred vision, nausea, loss of appetite, constipation, urinary retention, drowsiness, dizziness, depression and abdominal pain (references 2 and 3 of Sponsor, see last page of this review).

Watson Laboratories, Inc. (the sponsor) has developed a transdermal system for the delivery of oxybutynin (Oxybutynin TDS). TDS requires less frequent dosing, which is believed to increase the potential for improved patient compliance. The sponsor has submitted a phase II study (O096017) in which TDS oxybutyin treatment efficacy on urge urinary incontinence (UI) was compared with oral form and a phase III study (O099009) in which TDS oxybutynin treatment efficacy on improvement of number of UI per week was compared with placebo. This review pertains to these two studies.

2 INTRODUCTION

Overactive bladder is a disease state characterized by symptoms of urinary urge incontinence, frequency, and urgency. Urge incontinence refers to the involuntary loss of urine associated with a strong desire to void (urgency) and is usually associated with detrusor muscle instability. The bladder contractions caused by detrusor instability can result in urinary incontinence with or without a sense of urgency. Detrusor instability can also cause symptoms of urgency without concurrent urinary incontinence. Detrusor hyperreflexia may also lead to instability and incontinence in those patients with neurologic lesions such as stroke, multiple sclerosis, and spinal cord injury.

3 STUDY OVERVIEW

3.1 STUDY O99009

3.1.1 TRIAL DESCRIPTION

This was a 12-week multi-center (40 study sites), randomized, double-blind, placebo-controlled study with a 12-week open-label, dose-titration, safety period and a 28-week open-label safety extension in patients with urge urinary incontinence. Patients who met the eligibility criteria during the screening and baseline evaluations were randomized to one of the following treatment groups: 13 cm^2 Oxybutynin TDS, 26 cm^2 Oxybutynin TDS, 39 cm^2 Oxybutynin TDS, or placebo TDS. Doses were obtained using combinations of active and placebo 13 cm^2 and 26 cm^2 systems. All patients applied two systems, twice weekly (approximately every 3.5 days), to the abdomen for a total of 12 weeks. The active TDS delivered a nominal dose of 0.1 mg oxybutynin/cm^2 surface area per day. The double blind phase was initiated on December 21, 1999 and completed on July 26, 2000, and the 12-week open label safety phase was completed on October 09, 2000. The Statistical Analysis Plan (SAP) was finalized on May 02, 2000 and amended on August 10, 2000 to incorporate the addition of the 28-week safety extension period to the study.

The primary objective was to compare the safety and efficacy of 3 doses of oxybutynin transdermal delivery system (TDS) with placebo during 12 weeks of treatment and the secondary objective was to compare the daily urinary frequency, urinary volume per void, quality of life (QoL) scores, global assessment of disease state, as well as safety assessments. The primary efficacy endpoint was "the change from baseline to endpoint in the double-blind period in the number of urinary incontinent episodes per week recorded in the 7-day urinary diary by patients receiving active treatment versus those receiving placebo."

Patients who completed the double-blind period were eligible to enter the 12-week, open-label, dose-titration safety period. In the open-label safety period, all patients began treatment with a single 13 cm^2

oxybutynin TDS applied twice weekly. The dose of medication was titrated by the investigator after 2 and 4 weeks of treatment based on patients' symptoms and remained fixed for the last 8 weeks. For the open-label safety period, change from baseline to endpoint (week 24, visit 10 or LOCF) for the primary measurement was analyzed by final dose group. Characterization of the distribution of doses used by the patients in the study, confirmation of continued efficacy using both objective and subjective measures, and continued treatment safety in approximately 300 patients, changes in QoL scores over the 12-week open-label safety period, plasma concentrations of oxybutynin and its primary active metabolite were also of interest.

Patients who completed the 12-week open-label safety period had the option to continue into a 28-week, open-label, fixed-dose safety extension. Participation was limited to approximately 150 patients from the top-performing sites in order to ensure exposure in 100 patients. The results of the 28-week open-label safety extension were reported separately. The schedule of the trial can be found in Appendix A. **This review focuses on the double-blind phase of the study.**

STATISTICAL PLAN

No interim analyses were planned. The primary efficacy analysis compared the change in number of urinary incontinence episodes per week from baseline to endpoint using LOCF imputation for patients not completing the double-blind period. The number of episodes was obtained from 7-day urinary diary and was normalized to a 7-day value for patients with < 7 days of recorded data. This parameter was analyzed by ANCOVA, see Reviewer's evaluation and comments section in p.8-9.

SAMPLE SIZE ESTIMATION

The sponsor used the adjustment for three comparisons (i.e., each active dose level to placebo) each at 0.016 significance level and assumed a common standard deviation of 17 episodes per week. About 90 patients per treatment group was estimated to detect a difference between treatment groups of 10 episodes per week with 93% power.

URINARY DIARY

A 7-day urinary diary was used to record the time of normal voids, times of urinary incontinence, estimated amount of leakage, and etiology of incontinence episode (urge or stress). In addition, on two consecutive days during each diary period (a 48-hour period of the patient's choosing), patients were required to collect all urine during normal voids and record the voided volume. Patients must be individually trained on the use of the urinary diary and must practice recording urine volume during the baseline evaluation (Visit 2). Patients were required to visit the clinic upon completion of Weeks 3, 6, 9, and 12 (Visits 4 through 7) of the double-blind period of the study.

3.1.2 OVERVIEW OF SPONSOR RESULTS AND REVIEWER COMMENTS

PATIENT DISPOSITION

A total of 1129 patients were screened for participation in the study. Primary reasons for screen failure were patient decision not to participate (175) and failure to meet the required number of incontinence episodes (130). Five hundred and twenty patients were enrolled and randomized at 40 sites: 132 (25.4%) to receive placebo, 130 (25%) 13 cm^2 Oxybutynin TDS, 133 (25.6%) 26 cm^2 Oxybutynin TDS, and 125 (24%) 39 cm^2 Oxybutynin TDS. Four hundred forty-seven (86.0%) of the 520 treated patients completed the double-blind period. A total of 73 (14.0%) patients discontinued prematurely from the double-blind study. Table 6.1-1 summarizes patient disposition during the double-blind period and reasons for terminations. One patient (0403) moved to another site after Visit 4 and is referred to thro ughout the study as Patient 3219.

REVIEWER'S COMMENTS: It appeared that TDS Oxybutynin had more than twofold increase in percentage of patients dropping out from the study early as compared to placebo (16.1% vs. 7.6%). This result paralleled with the major reason of "due to adverse events" (12.1% vs. 4.5%).

Table 6.1 -1: Patient disposition – O99009 double-blind period

Disposition	Placebo	Oxybutynin		
		13 cm^2	26 cm^2	39 cm^2
Number of patients screened	1129			
Number (%) of patients randomized	132 (100%)	130 (100%)	133 (100%)	125 (100%)
Number (%) of patients treated	132 (100%)	130 (100%)	133 (100%)	125 (100%)
Number (%) of patients in mITT cohort	130 (98.5%)	130 (100%)	131 (98.5%)	124 (99.2%)
Number (%) of patients who completed period	122 (92.4%)	108 (83.1%)	110 (82.7%)	107 (85.6%)
Number (%) of patients who did not complete period	10 (7.6%)	22 (16.9%)	23 (17.3%)	18 (14.4%)
Reasons for not completing				
Adverse event	6 (4.5%)	15 (11.5%)	17 (12.8%)	15 (12.0%)
Protocol violation	1 (0.8%)	2 (1.5%)	1 (0.8%)	1 (0.8%)
Lost to follow up	1 (0.8%)	2 (1.5%)	2 (1.5%)	1 (0.8%)
Patient decision	2 (1.5%)	3 (2.3%)	2 (1.5%)	1 (0.8%)
Investigator decision	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)

Source: Report O99009, Tables 14.1.1.1.1 and 14.1.1.1.2; Listings 16.2.4.1.1 and 16.2.3.1.1

Note that of the 447 patients who completed the double-blind period and were eligible to continue into the open-label safety period, 411 (91.9%) patients entered the 12-week open-label safety period (Safety/ITT cohort). After dose titration, 61 (14.8%) patients received 13 cm^2 Oxybutynin TDS, 139 (33.8%) patients received 26 cm^2 Oxybutynin TDS, and 211 (51.3%) patients received 39 cm^2 Oxybutynin TDS as final doses in the 12-week open-label safety period.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients who participated in both the double-blind and open-label periods of the study were primarily elderly Caucasian women with a lengthy history of symptoms of overactive bladder, see Table 6.2-1. The overall study population included both men and women of Caucasian, Black, Asian/Pacific Islander, and Hispanic ethnicity. Patient age ranged from 20 to 88 years. The average age of the overall population was 61.4 ± 13.3 years with an average duration of incontinence of 9.2 years. All four treatment groups were comparable in demographic and baseline characteristics, including a history of risk factors contributing to a neurogenic etiology of disease and prior use of anticholinergic medications. According to the sponsor, age was the most commonly reported precipitating factor for overactive bladder symptoms.

The sponsor used two patient cohorts in the analysis of efficacy: the mITT and Evaluable cohorts. The mITT cohort (515 [99.0%] patients) was defined as all patients who received at least one application of a TDS and provided data for at least one efficacy assessment after the first application. There were 6 patients

with wrong treatment assignment during treatment randomization of the double-blind period, the treatment assignment used for analysis using the mITT cohort was the treatment actually received.

REVIEWER'S EVALUATION AND COMMENTS : This reviewer also analyzed the data using the ITT of the treatment actually assigned. In general, the results in terms of statistical significance were consistent between the sponsor's mITT cohort and this reviewer's as randomized analyses (rITT).

Table 6.2-1: Summary of patient demographics and duration of incontinence – O99009 double-blind period (Safety cohort)

Characteristic	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n	%	n	%	n	%	n	%
Number of Patients	132		130		133		125	
Gender								
Female	121	91.7	120	92.3	123	92.5	114	91.2
Male	11	8.3	10	7.7	10	7.5	11	8.8
Race								
Caucasian	118	89.4	119	91.5	118	88.7	118	94.4
Black	11	8.3	7	5.4	10	7.5	3	2.4
Hispanic	3	2.3	3	2.3	4	3.0	2	1.6
Geriatric Status								
<65 years	64	49.2	76	58.5	65	49.6	73	58.9
≥65 years	66	50.8	54	41.5	66	50.4	51	41.1
Age (years)								
Mean ± SD	62.7 ± 13.1		61.5 ± 11.8		61.9 ± 13.5		59.4 ± 14.5	
Range	30-88		28-87		26-84		20-86	
Duration of incontinence (months)								
Mean ± SD	109.7 ± 109.0		109.3 ± 123.5		106.3 ± 105.3		118.4 ± 117.7	
Range	6-600		6-780		5-600		6-564	

Source: Report O99009, Tables 14.1.2.1.1 and 14.1.3.1.2.1; Listing 16.2.5.1; Special Tables

EFFICACY EVALUATION

The primary efficacy analysis was to compare the change in number of urinary incontinence episodes from baseline to end of the double blind period (Week 12, Visit 7) using last observation carried forward (LOCF) imputation for patients not completing the double-blind period. The number of episodes was obtained from the 7-day urinary diary and was normalized to seven days for patients with less than seven days of recorded data.

Secondary efficacy analyses was to compare the mean change in average daily urinary frequency and the mean change in average urinary volume per void from baseline to the end of the double-blind period using LOCF imputation for patients not completing the double-blind period. Average daily urinary frequency was calculated by dividing the total number of events recorded on the 7-day urinary diary by the total number of days with data recorded in the diary. Average urinary volume per void was calculated by dividing the sum of the voided volumes by the total number of voids recorded during the 2-day urine volume documentation.

These parameters were analyzed using an analysis of covariance (ANCOVA) with the average daily baseline measure of that efficacy parameter as the covariate and effects of treatment and center. Hypothesis tests for each of the three active treatment effects compared to placebo were conducted using differences of adjusted means. To control the maximum experiment Type I error at α=0.05, the

comparisons were made using Dunnett's method. Treatment-by-center interaction was investigated as a secondary, exploratory analysis to assess homogeneity of treatment effects across centers.

The sponsor noted that "normality assumption of the parametric ANCOVA failed to hold, a ranking procedure was implemented based on the non-normal distributions. For the mITT cohort analysis of the primary efficacy parameter, change in number of urinary incontinence episodes per week, the equality of slopes assumption failed to hold at Visit 7. The analysis for this visit used the unequal slopes ANCOVA. For the mITT cohort analysis of the secondary efficacy parameter, change in average urinary volume per void, the equality of slopes assumption failed to hold at Visits 5, 6, and endpoint. Therefore, the analysis for these visits used the unequal slopes ANCOVA."

- **PRIMARY EFFICACY: Change in Number of Urinary Incontinence Episodes per Week**

During the double-blind period, patients in the mITT cohort treated with the 39 cm^2 TDS experienced a statistically significant decrease in the number of urinary incontinence episodes per week from baseline to endpoint ($p = 0.0165$) compared with placebo. The median number of incontinence episodes in the 39 cm^2 group decreased by 19 (61.3%) episodes per week compared with the median decrease of 14.5 episodes per week in the placebo group. No significant differences from placebo were found for the 13 cm^2 or 26 cm^2 treatment groups (a median decrease of 14.0 episodes per week in the 13 cm^2 group and 15.0 in the 26 cm^2 group).

The sponsor noted that 45 patients achieved complete continence: 10 in the placebo group, 12 in the 13 cm^2 treatment group, 7 in the 26 cm^2 treatment group, and 16 in the 39 cm^2 treatment group. Baseline values for the number of incontinence episodes per week and the change from baseline in response to treatment showed considerable interpatient variability. Patients at baseline reported a range of 2 to 163 episodes of incontinence per week. Minimum and maximum changes from baseline at endpoint wer — episodes for the placebo group, — episodes for the 13 cm^2 group, — episodes for the 26 cm^2 group, and — episodes for the 39 cm^2 group.

Table 7.2-1 summarizes the change in number of urinary incontinence episodes per week from baseline to endpoint in the double-blind period for the mITT cohort by treatment group. The mean number of urinary incontinence episodes per week is graphically displayed for the mITT cohort by visit and treatment group in Figure 11.4-1.

Table 7.2-1: Summary of number of urinary incontinence episodes per week at baseline and change from baseline to endpoint – double-blind period (mITT cohort)

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Number of urinary incontinence episodes per week								
Baseline (Visit 3)								
Mean and SD	37.7	24.0	38.2	26.2	36.2	22.8	34.9	18.4
Median	30.0		31.0		30.0		31.0	
Endpoint change from baseline								
Mean and SD	-19.2	21.1	-18.1	19.5	-17.2	18.3	-21.7	17.8
Median	-14.5		-15.0		-14.0		-19.0	
P-value[1]			0.9992		1.0000		0.0165	

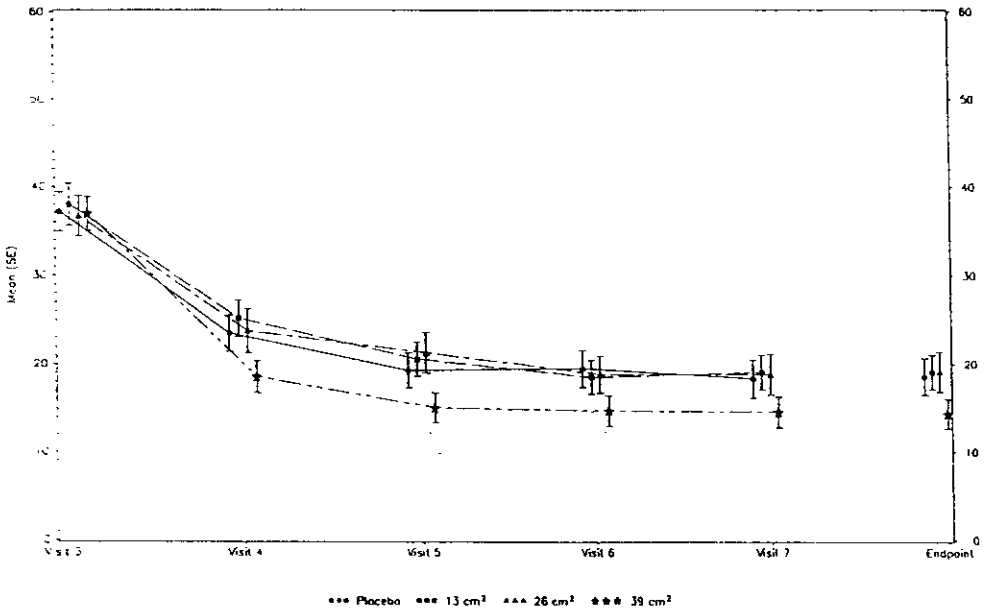
[1]Comparison significant if $p \leq 0.05$.

Source: Table 14.2.1.1.1.1; Listing 16.2.7.1.1

REVIEWER'S EVALUATION AND COMMENTS: This reviewer confirmed the above results. Note that the p-values were obtained from the contrast evaluation using Dunnett's adjustment.

The graphical presentation of the sponsor's results is shown in the sponsor Figure 11.4-1, which depicts the mean number of urinary incontinence episodes per week by visit and treatment groups during the double-blind period.

Figure 11.4 -1: Mean number of urinary incontinence episodes per week by visit and treatment group – double-blind period (mITT cohort)



REVIEWER'S EVALUATION AND COMMENTS

The protocol specified analysis is the usual parametric ANCOVA adjusting for baseline UI and pooled center. The sponsor has conducted several analyses in light of necessary assumptions for the analysis of covariance (ANCOVA) that may not be met for the primary efficacy outcome – change from baseline in the number of urinary incontinence episodes per week. The statistical evidence of treatment effect of 39 cm^2 oxybutynin varied from p=0.2831 (parametric ANCOVA) to p=0.0165 (non-parametric rank RT-2 ANCOVA). Using either the parametric or non-parametric ANCOVA analysis, 13 cm^2 and 26 cm^2 were not shown different from placebo. The median change from baseline of number of UI episodes per week was -14.5 (placebo group), -15.0 (13 cm^2 group), -14.0 (26 cm^2 group) and -19.0 (39 cm^2 group), respectively, based on all treated principle. As shown in the Sponsor Table 7.2-1, these ANCOVAs were performed adjusting for study sites in addition to adjusting for the baseline UI episodes. Site audits were conducted on 4 of the 40 study sites in order to ensure general regulatory compliance. A for-cause audit was conducted at Site 12. Excluding Site 12, a significant treatment effect of 39 cm^2 using the non-parametric approach was still obtained, but not the parametric approach.

- **Violation of assumptions for parametric ANCOVA**

This reviewer investigated the normality assumptions of the sponsor's originally proposed parametric ANCOVA method. It appeared that the distributions of "baseline urinary incontinence episodes", "its outcome measure", "change from baseline of number of urinary incontinence episodes per week" were not normal.

- **Baseline measurement**

This reviewer performed a global non-parametric test, which yielded a nominal p-value of 0.900, indicating no evidence against similar baseline urinary incontinence episodes among the four treatment groups.

- **Evaluation of robustness of the ANCOVA**

In the sponsor's non-parametric ANCOVA analysis, study site factor was a blocking factor. A total of 40 sites were pooled into 30 sites due to possible numerical imbalance of treatment assignment caused by small numbers of patients.

This reviewer further evaluated the data to investigate the robustness of the results using the non-parametric approach reported by the sponsor. This reviewer performed a non-parametric rank ANCOVA comparison without adjusting for the site. A significant treatment effect was observed only in the 39 cm^2 group either using mITT or rITT (Dunnett adjusted p-value 0.03), but not in the 13 cm^2 group or the 26 cm^2 group. In addition, this reviewer performed a simple comparison on percent change from baseline using the Kruskal-Wallis non-parametric approach without adjusting for the study site factor. The percent change from baseline of number of urinary incontinence per week is a standardized measurement, which makes the comparison in reference to patients' baseline measurement and measured in terms of percentages. This analysis showed that on the average, the 39 cm^2 Oxybutynin treated patients had 10 percent more reduction in urinary incontinence per week than the placebo treated patients (median: 73% reduction with 39 cm^2 vs. 63% reduction with placebo). But numerically worse percentages were observed in the 13 cm^2 (median: 58% reduction) and 26 cm^2 (median: 60% reduction) Oxybutynin TDS treated groups.

- **The sponsor was optimistic at the planning stage**

Using the Bonferroni adjustment for three comparisons (i.e., each active dose level to placebo), the significance level for each comparison being $\alpha = 0.016$, the sponsor assumed a common standard deviation (SD) of 17 episodes per week and 90 patients per treatment group in their sample size estimation. The sponsor anticipated a difference between treatment groups of 10 episodes per week could be detected with 93% power.

Apparently, the sponsor underestimated the SD. The empirical data showed that SD ranged from 18.4 to 26.2. In addition, the sponsor overestimated the treatment difference of 10 episodes per week, which was not supported by the empirical estimates (0 to 0.5 episodes per week with 26 cm^2 group and 13 cm^2 group to 4 episodes per week with 39 cm^2 group). Hence, the study appeared to be under powered for the observed treatment difference.

OTHER EFFICACY

- **Change in Average Daily Urinary Frequency**

Table 7.3-3 summarizes the change in average daily urinary frequency from baseline to endpoint in the double-blind period for the mITT cohort by treatment group. Patients in the double-blind period who were in the 39 cm^2 treatment group experienced a marginally significant decrease at endpoint in average daily urinary frequency when compared with placebo ($p = 0.0457$). The median decrease in urinary frequency was 2 episodes per day compared with a median decrease of 1 episode per day for placebo. The two remaining treatment groups showed no significant differences compared with the placebo group at any visit. Baseline values for the average daily urinary frequency and the change from baseline in response to treatment also showed considerable interpatient variability. Patients at baseline reported a range of 8 to 29 micturitions. Minimum and maximum changes from baseline at endpoint were — micturitions for the placebo treatment group. — micturitions for the 13 cm^2 group, — micturitions for the 26 cm^2 and — micturitions for the 39 cm^2 group.

Table 7.3-3: Summary of average daily urinary frequency and change from baseline to endpoint – double-blind period (mITT cohort)

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Daily urinary frequency (episodes)								
Baseline (Visit 3)								
Mean and SD	12.4	3.5	12.4	3.7	11.8	2.8	11.8	3.1
Median	11.0		11.0		11.0		11.0	
Endpoint change from baseline								
Mean and SD	-1.7	3.0	-1.8	2.6	-1.8	2.4	-2.3	2.5
Median	-1.0		-2.0		-2.0		-2.0	
P-value[1]			0.8292		0.3624		0.0457	

[1]Active treatment vs placebo. P-value derived from Dunnett's test. Comparison significant if $p \leq 0.05$.

Source: Table 14.2.1.1.2.1; Listing 16.2.7.1.1

REVIEWER'S EVALUATION AND COMMENTS : This reviewer confirmed the above results. However, when the analyses of change from baseline without site factor adjustment or of the percent change from baseline of average daily urinary frequency were performed, no consistent statistical significance for the 39 cm^2 treatment group was observed.

- Average Urinary Volume per Void

Table 7.3-5 summarizes the change in average urinary volume per void from baseline to endpoint during the double-blind period for the mITT cohort by treatment group. Notice that baseline values for the average urinary volume per void and the change from baseline in response to treatment showed considerable interpatient variability. Patients at baseline reported a range of 6-400 mL average volume per void. Minimum and maximum changes from baseline at endpoint were — mL for the placebo group, - — for the 13 cm^2 group, — mL for the 26 cm^2 group, and — mL for the 39 cm^2 group.

REVIEWER'S COMMENTS : One needs to be careful when reading the Sponsor's Table 7.3-5. In general, there was no statistical significance when equal slopes were assumed. The sponsor implemented a ranking procedure based on non-normal distributions, and adjustments for unequal slopes were used due to the non-linearity of responses in relationship to the covariate.

- **Global Assessment of Disease State**

The sponsor reported that patients experienced a decrease in score for the global assessment of disease state, but results did not reach statistical significance in the double-blind period. Global assessment of disease state was performed on a 100-point VAS, where 0 = "no symptoms of urge incontinence" and 100 = "worst ever."

Table 7.3-5: Summary of average urinary volume per void at baseline and change from baseline to endpoint – double-blind period (mITT cohort)

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Average urinary volume per void (mL)								
Baseline (Visit 3)								
Mean and SD	175.2	67.9	165.2	67.7	156.4	65.5	170.4	66.2
Median	168.0		163.0		147.0		168.0	
Endpoint change from baseline								
Mean and SD	12.8	59.1	8.8	67.6	25.1	58.0	31.8	67.6
Median	6.0		5.0		19.0		24.0	
P-value[1]			0.7379		0.0219*		0.0063*	

[1]Comparison significant if $p \leq 0.0167$

* Comparison for 26 cm^2 at endpoint significant for the 25 percentile value of the covariate ($p = 0.0008$) and the median ($p = 0.0157$) only using the unequal slopes model, for 39cm^2 at endpoint significant for the 25 percentile value of the covariate ($p = 0.0003$) and the median ($p = 0.0045$) only using the unequal slopes model.

Source: Table 14.2.1.1.3.1; Listing 16.2.7.1.1; Appendix 16.1.9.2.1.3, p. 150

EFFICACY: EXAMINATION OF REQUIRED SUBGROUPS

For the required subgroup analyses on gender, race (Caucasian versus non-Caucasian), and geriatric status (< 65 years of age versus ≥ 65 years of age), the sponsor noted that a large majority (more than 90%) of patients were Caucasian females. Only the geriatric (46%) and non-geriatric (54%) subgroups were of sufficient size to allow meaningful comparisons. For median change in incontinent episodes at endpoint, placebo response was greater in patients < 65 years of age (decrease of 15.5 episodes per week) compared with placebo patients ≥ 65 years of age (decrease of 13 episodes per week). Response to treatment in the 13 cm^2 and 39 cm^2 treatment groups was comparable with the overall population. Response in the 26 cm^2 group was greater in patients < 65 years of age (decrease of 15 episodes per week) compared with the geriatric population (decrease of 12 episodes per week). The geriatric patients exhibited a median decrease of 1 void per day compared with a median decrease of 2 voids per day in the non-geriatric subgroup in all treatment groups. Because females and Caucasians comprised the majority of patients in the study, results for these two subgroups mirrored the overall study results. Thus, no differences in efficacy were observed for subpopulations based on age, gender or race. Subpopulations in the study responded similarly to the population as a whole.

3.1.3 SUMMARY

The sponsor changed the study conduct to include the extended open-label safety study. In addition, the sponsor changed the planned analyses of parametric ANCOVA to non-parametric ranking procedure.

This reviewer confirmed "the distributional normality assumption of the parametric ANCOVA failed to hold for parameters based upon the diary data (change in number of urinary incontinence episodes per week, change in average daily urinary frequency, change in average urinary volume per void)." This reviewer performed a few analyses to investigate the robustness of the treatment effect of 39 cm^2 Oxybutynin relative to placebo based on "the change from baseline of the number of UI episodes per week". Placebo effects were observed. At the baseline, the median number of urinary incontinence per week was 30 to 31 among the four groups. In the 12-week double-blinded phase, placebo treated patients showed an improvement of 14.5 episodes less per week. In contrast, 15.0, 14.0, and 19.0 episodes less per

week were observed in the 13 cm^2, 26 cm^2 and 39 cm^2 groups, respectively. The results showed a marginal statistical significance of the 39 cm^2 Oxybutynin: the median improvement was less than one episode per day (or 0.64 episodes per day) equivalently, 4.5 episodes per 7 days. There were no consistent statistical evidence among the sensitivity analyses performed in the secondary efficacy outcomes of change in average daily urinary frequency and average urinary volume per void. In addition, there was no statistically significant finding with the global assessment of disease state. It is noted that there is only one phase III study in this submission.

3.2 STUDY O99017

3.2.1 TRIAL DESIGN SYNOPSIS

This study was a multi-center (12 centers), randomized, double-blind, controlled, dose-titration Phase II study. Eligible participants were patients diagnosed with urge incontinence associated with detrusor instability or detrusor hyperreflexia who had symptomatic improvement on prior treatment with oral oxybutynin. A total of 70 evaluable patients were expected to complete the study. Each eligible patient completed a urinary diary, an Anticholinergic Symptoms and Efficacy Questionnaire, and underwent a physical examination during baseline evaluation followed by a washout period of 1-2 weeks from current oral oxybutynin therapy (pretreatment period). Patients whose symptoms of incontinence worsened during discontinuation of oral oxybutynin underwent a cystometrogram and were eligible for the treatment phase. The two treatments included transdermal systems applied twice weekly (every 3.5 days) and oral capsules taken 2-3 times daily for 6 weeks. Each treatment included matching placebo and active formulations. Treatments were randomly assigned in a 1:1 ratio of transdermal:oral therapy. The dose of oxybutynin was titrated at the completion of 2 and 4 weeks of treatment based on the incidence and severity of adverse events. Patients completed a urinary diary and Anticholinergic Symptoms and Efficacy Questionnaire at the end of Weeks 2, 4 and 6, and underwent physical examination and cystometry at the end of the treatment phase. Treatment efficacy was determined based on the number of incontinence episodes at Week 6 compared to the pretreatment period. Statistical analysis was conducted to evaluate equivalence in efficacy between transdermal and oral oxybutynin therapy. Patient questionnaires on side effects, urodynamic variables, adverse events, skin tolerability, adhesive properties of the transdermal system, and plasma concentrations of oxybutynin were also evaluated.

The primary efficacy endpoint was the percentage of patients categorized as responders to treatment in each study group after a minimum of 4 weeks of treatment was established. Patients were categorized as responders or non-responders to treatment based on the difference in the number of incontinence episodes reported prior to and during treatment. Responders demonstrated a $\geq$ 30% decrease from baseline to endpoint in the number of daily incontinence episodes as recorded on their individual 3-day urinary diary. Patients were supplied with a urinary diary to take home at each clinic visit with instruction for completing the diary. Patients recorded each episode of urinary incontinence on 3 consecutive days. The time of each occurrence was recorded, along with an estimate of the amount of urine lost. The amount of urine was categorized on a scale from 1+ to 4+, increasing from a few drops to enough to run down the leg.

The secondary efficacy endpoints included a subjective overall rating of the efficacy of treatment based on current symptoms experienced by the patients and objective measures derived from the cystometrogram performed upon completion of treatment. 1) Visual analogue overall symptom scoring for urinary incontinence (leakage). 2) Maximum cystometric capacity (ml). 3) Volume at first detrusor contraction (ml). Response to treatment in secondary endpoints was evaluated as the change from baseline to endpoint. The primary safety variables were anticholinergic side-effects recorded by the patient at clinic visits.

3.2.2 *OVERVIEW OF SPONSOR RESULTS*

Table 5.2-1: Demographic summary of the ITT and evaluable patient populations

Parameter		Intent to Treat		Evaluable	
		Oral	Transdermal	Oral	Transdermal
Number		38	38	35	37
Age	Mean, SD	63 (14)	64 (15)	63 (13)	64 (15)
Race	Caucasian	36	36	34	35
	African Am.	2	2	1	2
Gender	Female	37	33	34	32
	Male	1	5	1	5
Incontinence History	Urge	37	36	34	35
	Mixed	1	2	1	2

Source: Table 8-4B, 8-4C

A total of 91 patients were screened. Of those, 76 patients were randomized to receive Oxybutynin either in TDS form (n=38) or oral form (n=38) for 6 weeks. Two patients were withdrawn after the fourth week, one from each treatment group. Patient #22 dropped from the oral treatment group due to intolerable dry mouth. Patient #67 withdrew from the study for personal reasons, relocation away from the study center. The patients were primarily elderly Caucasian women in either the ITT patients (n=76) or the evaluable patients (n=72), see Table 5.2-1.

According to the Sponsor, treatment compliance, assessed by returned unused medication, averaged greater than 95% of the expected medication use for both tablets and Oxybutynin TDS, see Table 6.3-3.

Table 6.3-3: Summary of treatment compliance (percent of expected use) – O96017 (Evaluable population)

Oxybutynin Formulation	Mean (SD) Compliance	
	Treatment Group	
	Oral	TDS
Capsule[1]	96 (10)	97 (8)
TDS[1]	101 (10)	97 (13)

[1] In order to maintain blind all treatment groups receive both capsule and TDS, one of which was placebo depending on treatment assignment.

Source: Report O96017, Table 8-6

The sponsor reported that 86% of transdermal treatment patients responded to treatment versus 89% in the oral group, yielding a 95% confidence interval for the mean difference of –17% to +13%, see the Sponsor Table 7.2-3). The sponsor also reported that "average (SD) incontinent episodes decreased from washout to Week 6 in both treatment groups: transdermal from 7.3 (4.5) to 2.4 (2.4); oral from 7.4 (4.1) to 2.6 (3.3). Patient rated (visual analog scale) control of urinary leakage significantly was reduced by both treatment comparing washout to last visit (p<0.0001), with no difference between treatments (p=0.9). Cystometry in both treatment groups reflected expected changes with oxybutynin treatment, increased volume to first detrusor contractions and increased maximum bladder capacity."

Table 7.2-3: **Response to treatment and 2-sided 95% confidence intervals for difference between transdermal and oral therapy at Weeks 2, 4, 6 and last study visit in the evaluable patients**

Treatment	Study Period	Responder		Non Responder	
		Count	Percent	Count	Percent
Oral (n=35)	Week 2	29	83	6	17
	Week 4	31	89	4	11
	Week 6	31	89	4	11
	Last Visit	31	89	4	11
Transdermal (n=37)	Week 2	25	68	12	32
	Week 4	29	78	8	22
	Week 6	30	86	5	14
	Last Visit	32	86	5	14
Transdermal vs Oral	**Study Period**	**Difference in % Response**		**Lower 95% Confidence Limit**	**Upper 95% Confidence Limit**
	Week 2	-15		-35	4
	Week 4	-10		-27	7
	Week 6	-3		-19	13
	Last Visit	-2		-17	13

Source: Table 8-7A

3.2.3 *REVIEWER'S EVALUATION AND COMMENTS*

The sponsor's primary and supporting efficacy variables were analyzed using the evaluable population. The protocol called for "Equivalence is determined when the 95% confidence limits for the difference in efficacy (proportion of responders) do not exceed 15%. A ninety-five percent confidence interval for the difference in proportion of responders between transdermal and oral oxybutynin were calculated, using a normal distribution approximation with estimates of standard errors based on observed proportions. There were no interim analyses planned. However, the sponsor reported that an interim assessment of the results of the study was conducted in August 1998, at which time approximately 50% of patients had completed the study. The sponsor stated that descriptive statistics for each treatment group were compiled for the number of incontinent episodes, the results of the anticholinergic questionnaires (dry mouth only), and adverse events. These results were reviewed by the senior management of TheraTech related to business decisions on the product development. Study personnel and investigators were not aware of these results.

The sponsor also performed an equivalence analysis based on the ITT patients. The results are summarized in the Sponsor Table below. If there were no interim analyses performed, the difference in responder rates between the TDS Oxybutynin and the oral Oxybutynin -2% with 95% CI of –20% to 10%, as shown in the last row of Sponsor Table below. The lower limit of the 95% CI was smaller than –15%, indicating that the TDS form is less effective by more than 15% compared to the oral form of Oxybutynin. The sponsor had performed one interim analysis at 50% of the recruitment. Using the conventional O'Brien-Fleming or Pocock's interim rule, the resulting lower limit of the 95% CI at last visit would be smaller than –20% or bigger than 20% in absolute value.

It is worthwhile noting that the sponsor's equivalence evaluation based on the evaluable patients failed to conclude that the TDS form would be equivalent to the oral form, because the lower limit of the 95% CI fell outside the equivalence limit of 15%. That is, the observed difference (TDS – ORAL) in responder rates was –2% with 95% CI of –17% and 13%. In fact, the results based on the ITT patients yielded a worst limit of –20%, which was worse than the evaluable patients of –17%. Thus, the study failed to conclude that TDS form is equivalent to the oral form.

This reviewer further investigated the possible reasons of the finding. In the protocol plan, sample size calculations were based on the assumption of a true proportion of responders to transdermal and oral being 95%. Nonetheless, the observed responder rates were only 84% (TDS) and 89% (oral) with the ITT

analysis and were 86% (TDS) and 89% (oral) with the evaluable analysis, respectively. With a patient size of 38 per arm, an equivalence margin of 15% provided the true responder rate of 95% would be under powered if indeed such an effect size would be clinically meaningful.

Sponsor Table: Analysis of Response by Treatment ITT Patients at Last Visit*

Treatment	Responder		Non-Responder	
	Count	Percent	Count	Percent
Oral (n=38)	34	89	4	11
Transdermal (n=38)	32	84	6	16
Transdermal vs Oral	**Difference in % Response**		**Lower 95% Confidence Limit**	**Upper 95% Confidence Limit**
	-5		-20	10

* Extracted from the Sponsor Table 8-7B, volume #135.

3.2.4 SAFETY EVALUATION

The primary safety variables were anticholinergic side effects recorded by the patient at clinic visits. Patients completed the anticholinergic questionnaires during clinic visits at baseline, washout, and study Weeks 2, 4, and 6. Patients were asked a series of questions about each symptom. This included the presence or absence of each specific symptom and its severity; to report if they had the symptom during prior oxybutynin treatment; and if the symptom was present prior to the study to comment on whether the current symptom was improved, the same, or worse than before. The ratings of mild, tolerable, and intolerable were used to guide decisions on dosing adjustments. Intolerable symptoms resulted in a dosing adjustment to reduce the severity of the symptom.

From these Questionnaires, the sponsor reported that dry mouth occurred in significantly fewer patients in the transdermal treatment group compared to the oral treatment group at every evaluation time point following the start of treatment ($p<0.001$, X^2 test). The other anticholinergic symptoms showed smaller differences between treatments compared to dry mouth. Dry mouth occurred in significantly fewer patients in the transdermal compared to the oral treatment group at every evaluation time point following the start of treatment ($p<0.001$, X^2 test). Oral treatment resulted in dry mouth symptoms in 82-94% of patients compared to 37-43% of the patients receiving transdermal therapy (see Sponsor Table 6.3-1). The majority of patients who reported dry mouth in the transdermal group experienced mild symptoms and no patients reported intolerable dry mouth.

The remaining space of this page is purposely left blank

Table 6.3-1: Frequency distribution of dry mouth symptoms by treatment in the evaluable patients

Study Period	Response	Severity	Oral		Transdermal	
			Count	Percentage	Count	Percentage
Baseline	No	---	4	12	5	14
	Yes	---	30	88	32	86
		Missing	1	3	1	3
		Mild	8	23	4	11
		Tolerable	15	43	24	65
		Intolerable	6	17	3	8
Washout	No	---	20	57	21	58
	Yes	---	15	43	15	42
		Missing	2	6	2	6
		Mild	7	20	5	16
		Tolerable	5	14	5	16
		Intolerable	1	3	1	3
Last Visit	No	---	2	6	23	62
	Yes	---	33	94	14	38
		Missing	1	3	0	0
		Mild	9	26	10	27
		Tolerable	20	57	4	11
		Intolerable	3	9	0	0

Note: For individual study periods, total numbers of patient reports reflect missing reports by some patients. Patients may have failed to respond to dry mouth question regarding occurrence of dry mouth and/or rating of severity of current symptom. *Source: Tables 8-23A, 8-23C*

3.2.5 SUMMARY

In this phase II, double-blind, active controlled trial, the difference in responder rates between the TDS Oxybutynin and the oral Oxybutynin was –2% with 95% CI of –17% to 13%, the lower limit of the 95% CI clearly fell outside the equivalence margin of 15%. By the protocol definition, the study failed on the primary efficacy outcome, the responder rate, based on the evaluable patients. The sponsor also reported the results based on the ITT patients. The difference in responder rates (TDS – oral) was –5% with 95% CI of –20% to 10%. The lower limit of the 95% CI was worse with the ITT analysis (-20%) than the evaluable analysis (-17%). Hence, from the pre-specified statistical criteria, the study failed to conclude that responder rate in TDS Oxybutynin treated group is equivalent to the oral Oxybutynin treated group based on either the evaluable patients or the ITT patients.

4 CONCLUSION

Oxybutynin TDS administered in three dosage strengths, 13 cm^2, 26 cm^2 and 39 cm^2, in a twice-weekly regimen was shown to be marginally effective for the 39 cm^2 Oxybutynin treated group compared to placebo during chronic treatment in patients with overactive bladder in one placebo-controlled double-blind Phase III trial. The median improvement in the 39 cm^2 Oxybutynin treated group was less than one episode reduction per day (or 0.64 episodes per day) or equivalently, 4.5 episodes reduction per 7 days compared with placebo. Clinical significance of such a small effect must be assessed by the medical review team, as there were no consistent statistical evidences among the results of the sensitivity analyses performed in the secondary efficacy outcomes of change in average daily urinary frequency and average urinary volume per void. In addition, there was no statistically significant finding with the global assessment of disease state.

A supportive phase II, double-blind, active controlled study failed to show that TDS Oxybutynin is equivalent to oral Oxybutynin on the primary efficacy outcome – responder rate with 15% equivalence margin, based on the evaluable patients or the ITT patients with or without interim analysis performed.

Sue-Jane Wang, Ph.D.
Senior Mathematical Statistician

Concur: S. Edward Nevius, Ph.D.
Division Director, HFD-715

Mike Welch, Ph.D.
Statistical Team Leader of HFD-580

cc:
Archival NDA# 21-351
HFD-580/Hirsch, Gierhart, Farinas
HFD-715/Anello, Nevius, Welch, Wang

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A. Schedule of Events (Study O099009)

Table 3-A Schedule of Events (Study O099009)

Assessments	Screening Period				Treatment Period								
					Double-Blind				Open-Label			Extension	
					Weeks *(days)*								
	Initial Evaluation	Wash-out[1]	Start of Baseline Evaluation[2]	End of Baseline Evaluation[3]	3	6	9	12	2	4	12	14	28
Days	*-22*	*-21 to -9*	*-8 to -2*	*0 to 1*	*2 to 21*	*22 to 42*	*43 to 63*	*64 to 84*	*1 to 14*	*15 to 28*	*29 to 84*	*1 to 98*	*99 to 196*
Patient Visits	V_1	2-week Washout/Training Period	V_2	V_3	V_4	V_5	V_6	V_7	V_8	V_9	V_{10}	V_{11}	V_{12}
Informed Consent	X												
Medical History	X												
Physical Examination				X				X			X		X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis			X					X			X		X
ECG				X[7]				X			X		X
Serum Chemistries (fasting)			X					X			X		X
CBC			X					X			X		X
PSA (Males only)			X										
Urine beta-HCG[4]			X					X			X		X
7-Day Urinary Diary[5]			X		X	X	X	X			X		
2-Day Voided Volume[6]			X		X	X	X	X			X		
PVR				X				X			X		
QoL Questionnaires													
SF-36				X				X			X		
UDI & IIQ				X		X		X			X		
Global Assessment				X				X			X		
Plasma Concentration				X		X		X			X		
Study Drug Dispensed				X	X	X	X	X	X	X	X	X	
Skin Tolerability Assessment					X	X	X	X	X	X	X	X	X
Adhesion Assessment					X	X	X	X	X	X	X	X	X
AE Assessment					X	X	X	X	X	X	X	X	X

[1] A 2-week wash-out period is required for any patient who is on urinary incontinence pharmacological treatment. All patients must undergo a 2-week training period for bladder and fluid management. Patients using non-pharmacological treatments, such as biofeedback, must have completed training at least two weeks prior to the baseline evaluation.

[2] Baseline Evaluation period begins after the 2-week discontinuation of urinary incontinence pharmacological treatment. During the Baseline Evaluation period, patients must complete the 7-day urinary diary. Patients who fail to meet the urinary diary criteria may be allowed to repeat the diary evaluation. Data collected after the first urinary diary period will be recorded on Visit 3A. Data collected for the second attempt will be recorded on Visit 3B.

[3] Prior to randomization, the patient's diary card must be faxed to — for review; the patient may be randomized once approval is received from —.

[4] Urine beta-HCG tests will be performed only for female patients of childbearing potential.

[5] A 7-day (consecutive days) urinary diary will be recorded during the week immediately prior to the indicated visit beginning at least eight days prior to the visit. The information will be evaluated by the site at each visit and transcribed onto the CRF.

[6] During 2 consecutive days of the 7-day diary, patients will be required to collect all urine during normal voids and record the voided volume on the diary card.

[7] The baseline ECG with 1-minute rhythm strip may be performed at either Visit 2 or Visit 3.

REFERENCE

(2) Moore KH, Hay DM, Imrie AE, Watson A, Goldstein M. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. Br J Urol 1990;66:479-85.

(3) Tapp AJS, Cardozo LD, Versi E, Cooper D. The treatment of detrusor instability in postmenopausal women with oxybutynin chloride: a double-blind placebo controlled study. Br J Obstet Gynaecol 1990;97:521-6.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sue Jane Wang
2/28/02 10:33:09 AM
BIOMETRICS

Mike Welch
2/28/02 10:55:56 AM
BIOMETRICS
Concur with review

S. Edward Nevius
3/12/02 10:26:37 AM
BIOMETRICS
Concur with review.

STATISTICAL REVIEW AND EVALUATION

Pediatric Study

IND#:	NDA 21-351
Sponsor:	Watson Laboratories Inc.
Name of Drug:	Oxytrol (oxybutynin transdermal ssytem)
Indication:	overactive bladder in the pediatric population
Document:	Pediatric development plan and protocol synopsis dated September 4, 2001
Medical Officer:	Brenda S. Gierhart, M.D. and Mark Hirsh, M.D. (HFD-580)

BACKGROUND

In response to FDA's notification that the information regarding pediatric studies submitted in the original NDA 21-351 was insufficient, the sponsor submitted (1) pediatric development plan, (2) timeline, (3) justification for the age and dose selection, and (4) protocol synopsis. In this same submission, the sponsor requested a partial waiver from pediatric studies for children under the age of six and a deferral of pediatric studies until approximately March 2003. This review pertains to the pediatric protocol synopsis.

REVIEWER COMMENTS

REVIEWER'S COMMENTS

This reviewer concurs with the medical reviewer and believes that the actual protocol should be submitted for review. Particularly, the design section and statistical section need be consistent and clearly stated.

Sue-Jane Wang, Ph.D.
Senior Mathematical Statistician

Concur: Mike Welch, Ph.D.
Mathematical Statistician (Team Leader)

NDA 21-351
HFD-170 Gierhart/Hirsch/Farinas, HFD-715 Welch/Wang
SWANG/301-827-3089/10-11-2001/oxybutynin_pediatrc.doc
This review consists of 1 pages of text.