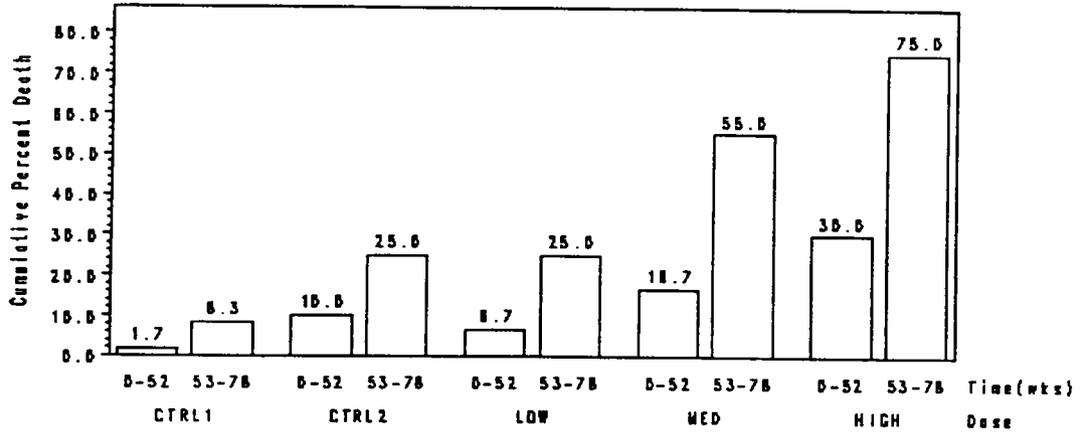


Figure 1a

Cumulative Percent of Death

Species: Mouse
Sex: Male

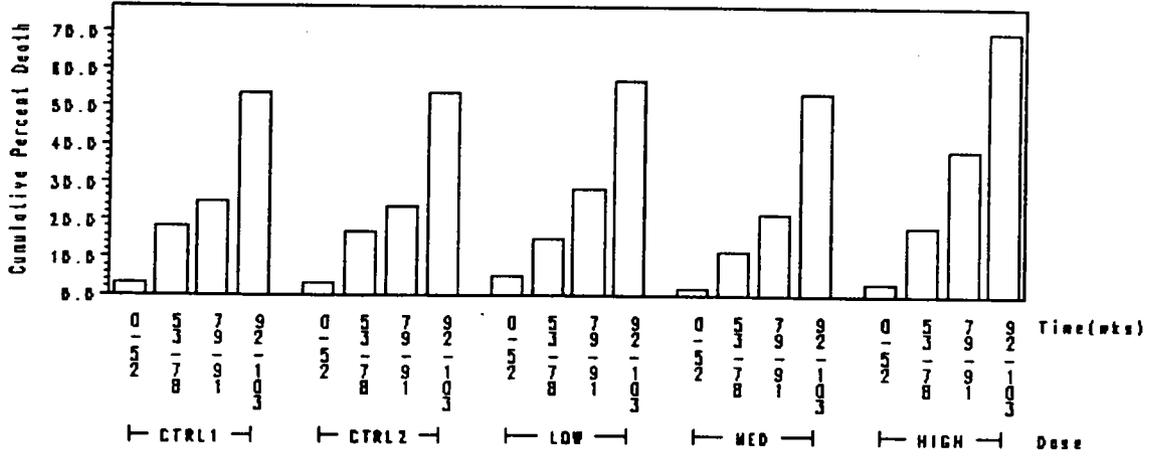


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ON ORIGINAL

Figure 1b

Cumulative Percent of Death

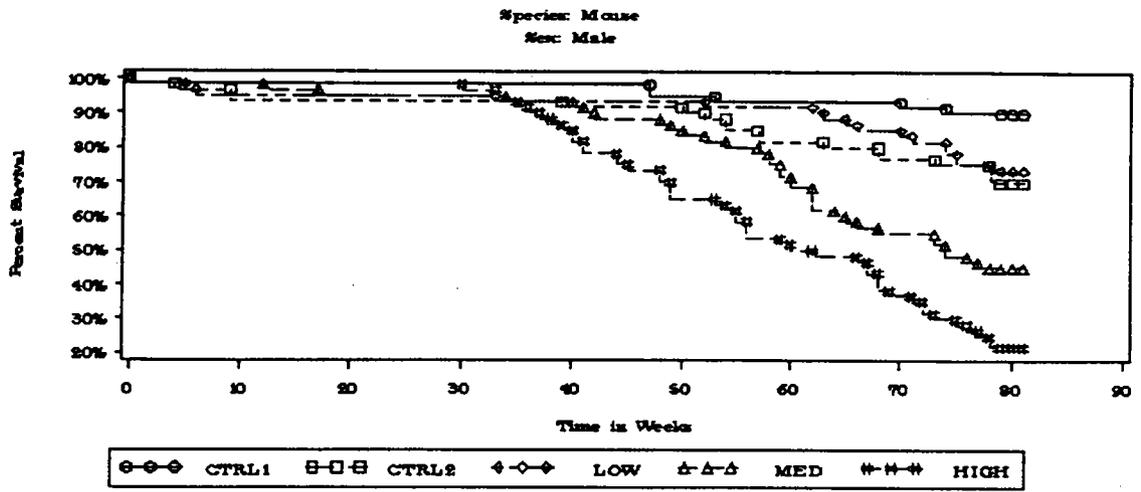
Species: Mouse
Sex: Female



APPEARS THIS WAY
ON ORIGINAL

Figure 2a

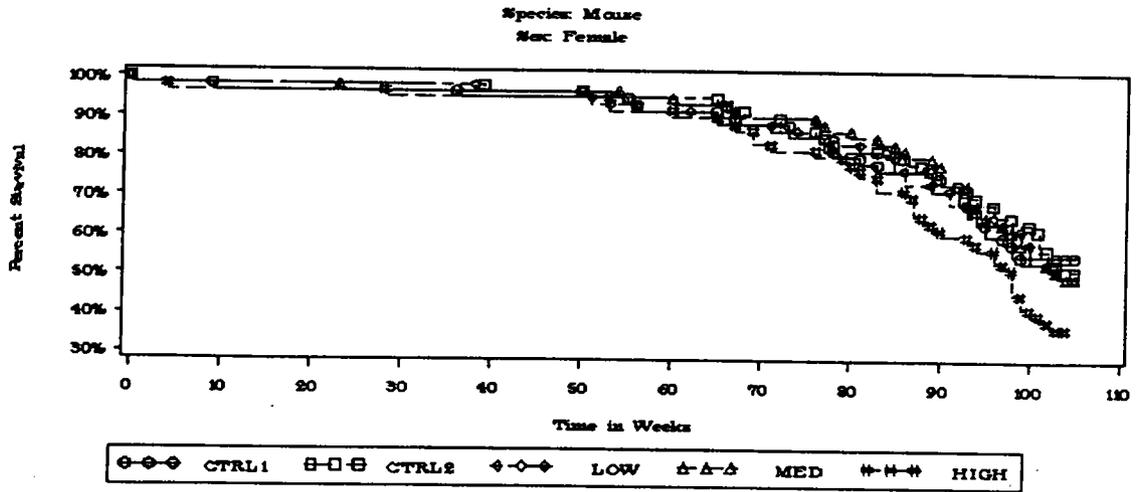
Kaplan—Meier Survival Function



APPEARS THIS WAY
ON ORIGINAL

Figure 2b

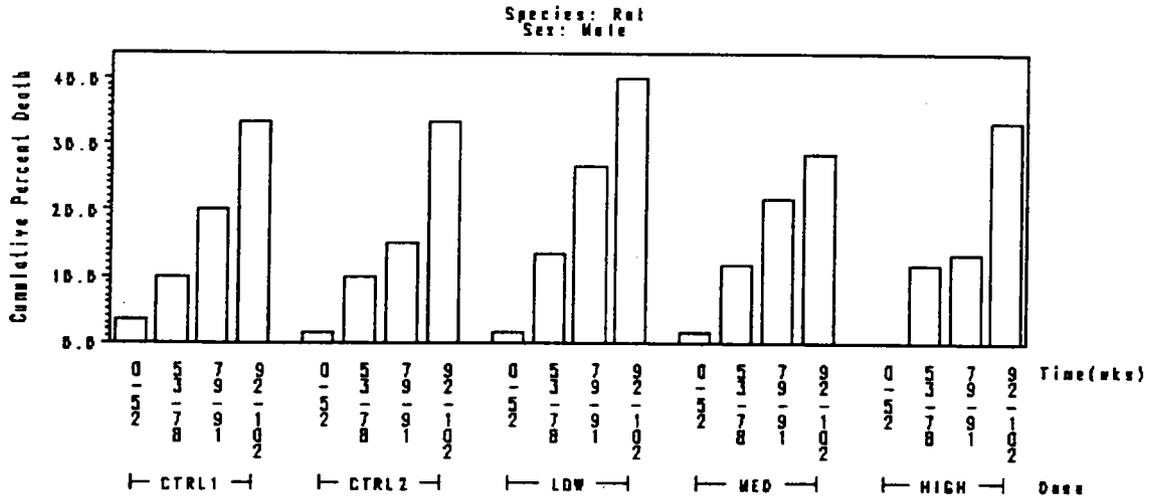
Kaplan—Meier Survival Function



APPEARS THIS WAY
ON ORIGINAL

Figure 3a

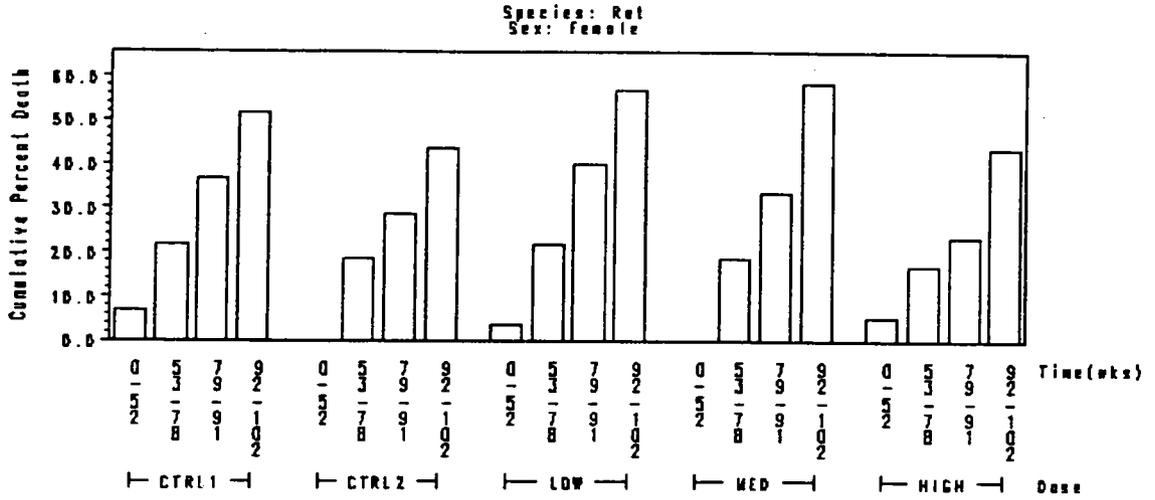
Cumulative Percent of Death



APPEARS THIS WAY
ON ORIGINAL

Figure 3b

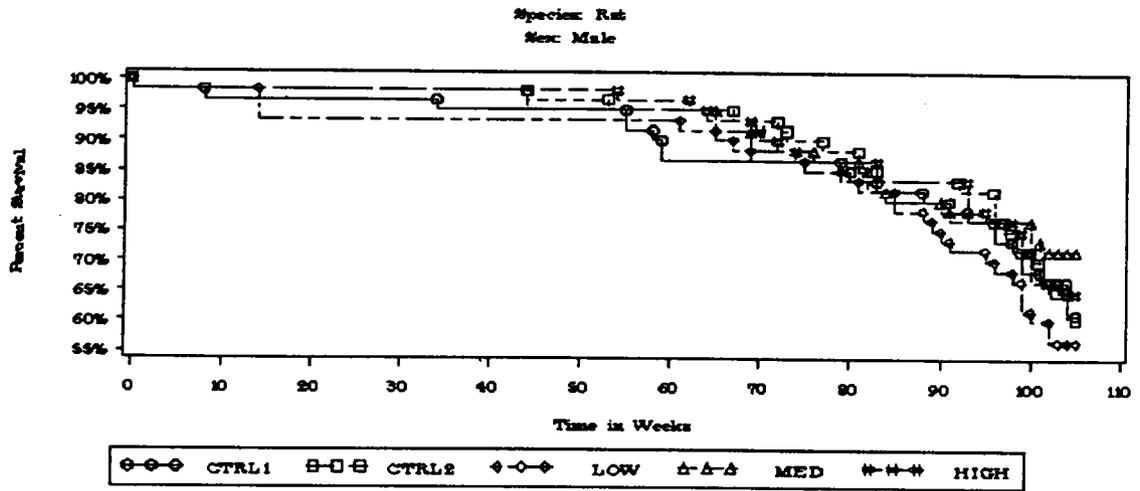
Cumulative Percent of Death



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IN ORIGINAL

Figure 4a

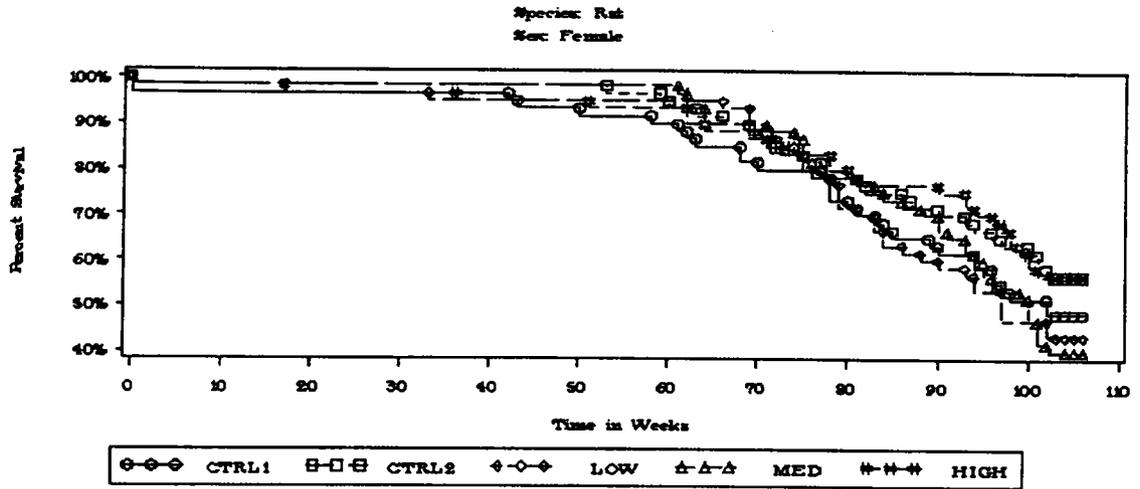
Kaplan—Meier Survival Function



APPEARS THIS WAY
ON ORIGINAL

Figure 4b

Kaplan—Meier Survival Function



APPEARS THIS WAY
ON ORIGINAL

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**STATISTICAL REVIEW AND EVALUATION
(Clinical)**

NDA #: 20-771/Drug Class 1S

APPLICANT: Pharmacia & Upjohn

NAME OF DRUG: Detrusitol Tablets (Tolterodine)

INDICATION: Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

DOCUMENTS REVIEWED: Volumes 1.1, 1.2, 1.198 through 1.285

MEDICAL REVIEWER: Daniel Shames, MD (HFD-580).

I. Background

There were 4 controlled studies of 12-week duration. Three of them (studies 008, 009, and 010) were placebo-controlled studies. The fourth study (study 015) was an active-controlled study conducted with an objective of showing equivalence of tolterodine 2 mg bid with oxybutynin 5 mg tid. This review includes the evaluation of the three placebo-controlled studies and excludes the evaluation of the active-controlled study as data from this study does not support the equivalence of tolterodine 2 mg bid with oxybutynin 5 mg tid for all the efficacy variables.

The protocols for placebo-controlled studies 008 and 010 were similar in design. These studies were multicenter, multinational, randomized, double-blind, double dummy studies comparing tolterodine with oxybutynin and placebo. The purpose of including oxybutynin in these studies was to show an equivalence with tolterodine. These studies were powered for detecting a difference between tolterodine and placebo and an equivalence between oxybutynin and tolterodine. Study 009 was a multicenter, multinational, randomized, double-blind study comparing tolterodine 1 mg bid and tolterodine 2 mg bid with placebo. This study was powered for detecting a difference between tolterodine (1 mg or 2 mg dose) and placebo.

In these studies, patients were randomized after a two-week wash-out period to 12-week study. Those who completed the full study period were allowed to participate in an open label nine-month follow-up study. The primary endpoint was mean reduction in micturitions per 24 hours from baseline to 12 weeks. Among several secondary endpoints, important ones were mean reduction in incontinence episodes per 24 hours and change in mean volume voided per micturition. Analysis of the intent-to-treat (ITT) population was the primary analysis. The ITT analysis was performed using the last-observation-carried-forward or, where necessary, the first observation carried backward.

This review is focused on the evaluation of three studies (namely 008, 009 and 010) for three efficacy variables: number of micturitions per 24 hours, number of incontinence episodes per 24 hours and volume voided per micturition for the ITT population. Section II provides sponsor's analyses and results; section III gives this reviewer's analyses and results; and section IV contains this reviewer's conclusions.

II. Sponsor's Analyses and Results (008, 009, 010 and 015)

The sponsor utilized a parametric approach to analyze the data. In order to validate the accuracy of data, this reviewer was able to reproduce the sponsor's results for Study 008.

The efficacy variables were analyzed using an ANOVA with factors for treatment group, visit and patient within treatment and a treatment-by-visit interaction in the model. As these were multicenter studies, a model involving a center factor and a treatment-by-center interaction was also analyzed. Hypothesis testing was conducted using Type III sum of squares in SAS/PROC GLM. Treatment comparisons were performed with appropriate contrasts using adjusted means.

Study 008

In Study 008, 293 patients were randomized to treatment with tolterodine 2 mg bid, oxybutynin 5 mg tid or placebo in the ratio of 2:2:1 at 42 centers (23 in UK, 4 in Ireland, 15 in Sweden).

Patient Disposition

Patient disposition results for ITT population are given in the following table.

Study 008: Patient Disposition

No. of Patients	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
Randomized	57 (100%)	118 (100%)	118 (100%)
Completed	50 (87.7%)	104 (88.1%)	92 (78%)
Withdrawn	7 (12.3%)	14 (11.9%)	26 (22%)

(Source: Table 16, vol. 1.2)

Baseline Comparison

The following table provides descriptive statistics for baseline comparison. Mean BMI (Body Mass Index) and mean age were similar across the treatment groups. There was a greater percentage of females compared with males and Caucasians compared with Non-Caucasians.

Study 008: Baseline Comparison

Variable	Placebo		Tolterodine 2 mg		Oxybutynin	
	N	Mean (Range)	N	Mean (Range)	N	Mean (Range)
BMI (kg/m ²)	57	27.7 ()	118	26.8	118	26.9
Age (yr.)	57	58.2	118	55.3	118	57.6
	n	%	n	%	n	%
Gender						
Male	14	24.6%	27	22.9%	30	25.4%
Female	43	75.4%	91	77.1%	88	74.6%
Race						
Caucasian	56	98.2%	117	99.2%	117	99.2%
Non-Caucasian	1	1.8%	1	0.8%	1	0.8%

(Source: Table 14, vol. 1.2)

Efficacy Analysis

Mean Number of Micturitions per 24 Hours

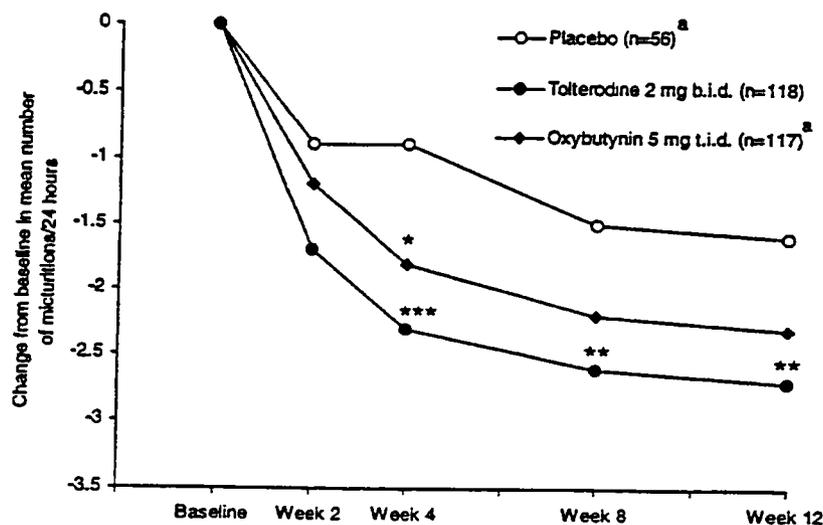
The results of the statistical analyses for the mean number of micturitions per 24 hours at baseline and Week 12 are presented in the following table and figure.

Study 008: Mean Number of Micturitions per 24 Hours

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	56 (1)	118 (0)	117 (1)
Baseline			
Mean (SD)	11.7 (4.9)	11.5 (4.4)	10.7 (3.3)
Range			
Week 12			
Mean (SD)	10.2 (4.1)	8.8 (2.9)	8.4 (2.8)
Range			
Chg. From Baseline at Week 12			
Mean (SD)	-1.6 (3.6)	-2.7 (3.8)	-2.3 (2.7)
Range			
Difference from Placebo			
Mean Difference (SEM)		1.2 (0.4)	-0.7 (0.4)
p (Appropriate Contrast)			

(Source: Table 16, vol. 1.2)

The following figure provides the results at baseline and Weeks 2, 4, 8, and 12 for the ITT population. The sponsor stated that the difference in reduction from baseline after 12 weeks of treatment in the mean number of micturitions per 24 hours was statistically significant in favor of tolterodine 2 mg bid compared with placebo. The p-values were not adjusted for multiple comparisons.



^a One patient missing due to missing micturition chart data

* 0.01 < p ≤ 0.05, ** 0.001 < p ≤ 0.01, *** p ≤ 0.001, difference vs. placebo

Mean Number of Incontinence Episodes per 24 Hours

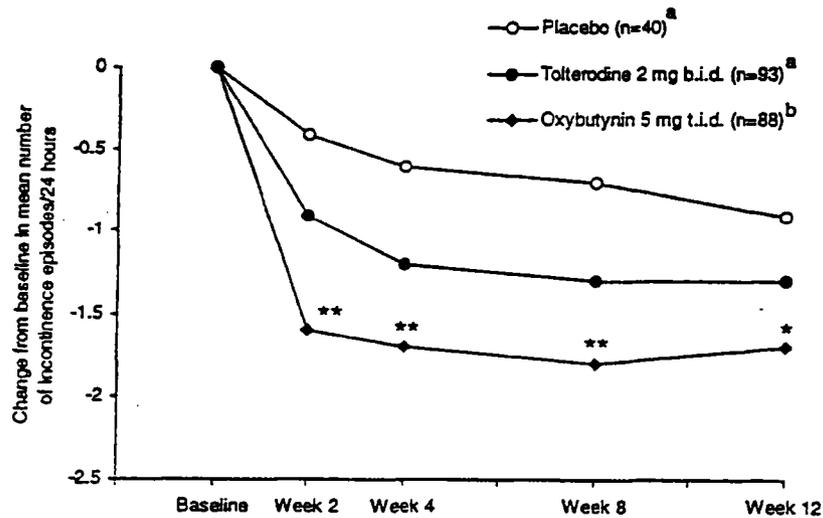
The results of the statistical analyses for the mean number of incontinence episodes per 24 hours at baseline and Week 12 are presented in the following table and figure. Patients without incontinence episodes at baseline are not included in the table and figure.

Study 008: Mean Number of Incontinence Episodes per 24 Hours

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	40 (2)	93 (1)	88 (2)
n (patients without incontinence at baseline)	15	24	28
n (patients who developed incontinence during study)	3	6	5
Baseline Mean (SD) Range	3.3 (3.9)	2.9 (3.1)	2.6 (3.3)
Week 12 Mean (SD) Range	2.4 (4.0)	1.6 (2.3)	0.9 (1.5)
Chg. From Baseline at Week 12 Mean (SD) Range	-0.9 (1.5)	-1.3 (3.2)	-1.7 (3.1)
Difference from Placebo Mean Difference (SEM) p (Appropriate Contrast)		-0.5 (0.4)	-0.9 (0.4)

(Source: Table 19, vol. 1.2)

The following figure provides the results at baseline and weeks 2, 4, 8, and 12 for the ITT population. The sponsor stated that the difference in reduction from baseline after 12 weeks of treatment in the mean number of incontinence episodes per 24 hours was not statistically significant in favor of tolterodine 2 mg bid compared with placebo.



^a Two patients missing due to missing micturition chart data.
^b One patient missing due to missing micturition chart data.
 ** 0.001 < p < 0.01, difference vs. placebo

Mean Volume Voided per Micturition (ml)

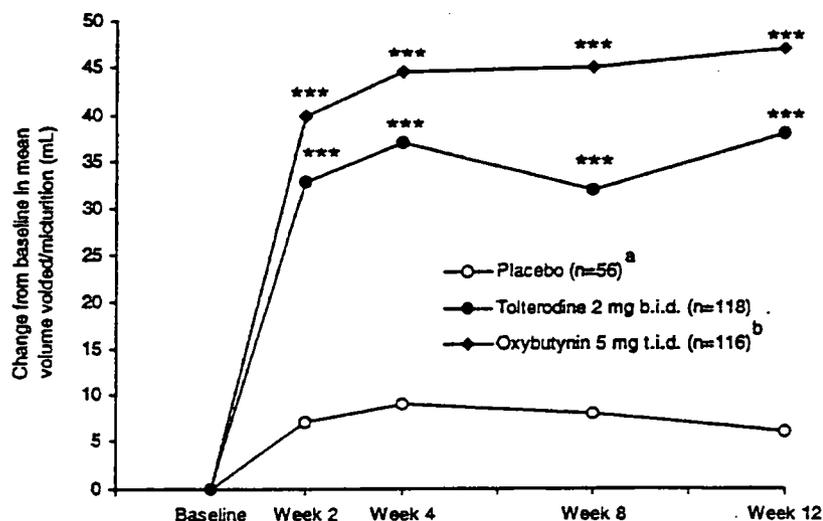
The results of the statistical analyses for the mean volume voided per micturition (ml) per 24 hours at baseline and Week 12 are presented in the following table and figure.

Study 008: Mean Volume Voided per Micturition

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	56 (1)	118 (0)	116 (2)
Baseline			
Mean (SD)	157 (63)	166 (61)	176 (62)
Range			
Week 12			
Mean (SD)	163 (69)	204 (75)	222 (83)
Range			
Chg. From Baseline at Week 12			
Mean (SD)	6 (42)	38 (54)	47 (58)
Range			
Difference from Placebo			
Mean Difference (SEM)		32 (7)	41 (7)
p (Appropriate Contrast)		0.0001	0.0001

(Source: Table 22, vol. 1.2)

The following figure provides the results at baseline and Weeks 2, 4, 8, and 12 for the ITT population.



a One patient missing due to missing micturition chart data.
 b Two patients missing due to missing micturition chart data.
 *** $p < 0.001$, difference vs. placebo

The sponsor stated that the difference in increase from baseline after 12 weeks of treatment in the mean volume voided per micturition was statistically significant in favor of tolterodine 2 mg bid compared with placebo. The p-values were not adjusted for multiple comparisons.

Study 009

In Study 009, 316 patients were randomized to treatment with tolterodine 1 mg bid, tolterodine 2 mg bid or placebo in the ratio 2:2:1 at 25 centers (18 in USA, 7 in Australia).

Patient Disposition

Patient disposition results for ITT population are given in the following table.

Study 009: Patient Disposition

No. of Patients	Placebo	Tolterodine 1 mg	Tolterodine 2 mg
Randomized	64 (100%)	123 (100%)	129 (100%)
Completed	61 (95.3%)	116 (94.3%)	114 (88.4%)
Withdrawn	3 (4.7%)	7 (5.7%)	15 (11.6%)

(Source: Table 13, vol. 1.2)

Baseline Comparison

The following table provides descriptive statistics for baseline comparison.

Study 009: Baseline Comparison

Variable	Placebo		Tolterodine 1 mg		Tolterodine 2 mg	
	N	Mean (Range)	N	Mean (Range)	N	Mean (Range)
BMI (kg/m ²)	64	26.8	123	28.0	129	27.3
Age (yr.)	64	60.5	123	60.1	129	60.2
	n	%	n	%	n	%
Gender						
Male	22	34.4%	27	22.0%	30	23.3%
Female	42	65.6%	96	78.0%	99	76.7%
Race						
Caucasian	59	92.2%	117	95.1%	126	97.7%
Non-Caucasian	5	7.8%	6	4.9%	3	2.3%

(Source: Table 14, vol. 1.2)

Mean BMI (Body Mass Index) and mean age were similar across the treatment groups. There was a greater percentage of females compared with males and Caucasians compared with Non-Caucasians.

Efficacy Analysis

Mean Number of Micturitions per 24 Hours

The results of the statistical analyses for the mean number of micturitions per 24 hours at baseline and Week 12 are presented in the following table and figure.

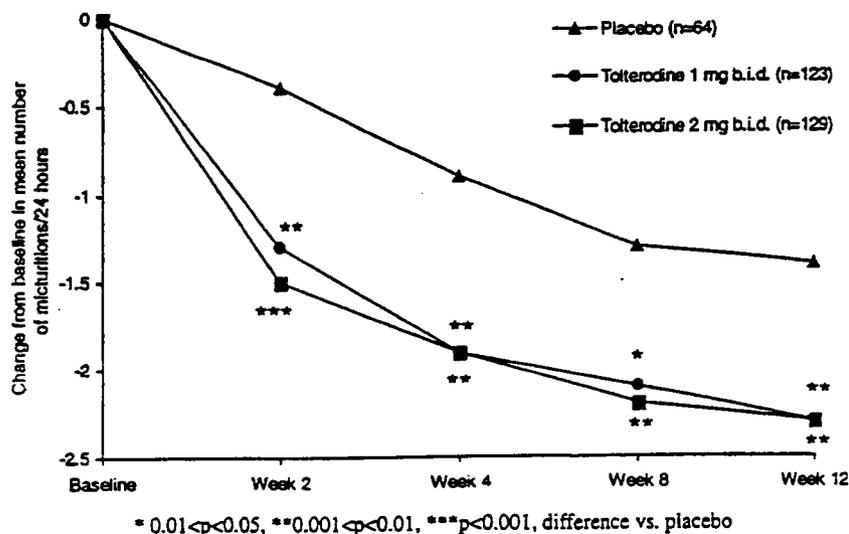
Study 009: Mean Number of Micturitions per 24 Hours

	Placebo	Tolterodine 1 mg	Tolterodine 2 mg
N (Missing Data)	64 (0)	123 (0)	129 (1)
Baseline			
Mean (SD)	11.3 (3.4)	11.5 (3.7)	11.2 (3.1)
Range			
Week 12			
Mean (SD)	9.9 (3.0)	9.2 (2.8)	9.0 (2.6)
Range			
Chg. From Baseline at Week 12			
Mean (SD)	-1.4 (2.3)	-2.3 (3.0)	-2.3 (2.1)
Range			
Difference from Placebo			
Mean Difference (SEM)		-0.9 (0.3)	-0.9 (0.3)
p (Appropriate Contrast)		0.0029	0.0045

(Source: Table 17, vol. 1.2)

The following figure provides the results at baseline and Weeks 2, 4, 8, and 12 for the ITT population. The sponsor stated that the difference in reduction from baseline after 12 weeks of treatment in the mean number of micturitions per 24 hours was statistically significant in favor of both tolterodine 1 mg bid compared with placebo

and tolterodine 2 mg bid compared with placebo. The p-values were not adjusted for multiple comparisons.



Mean Number of Incontinence Episodes per 24 Hours

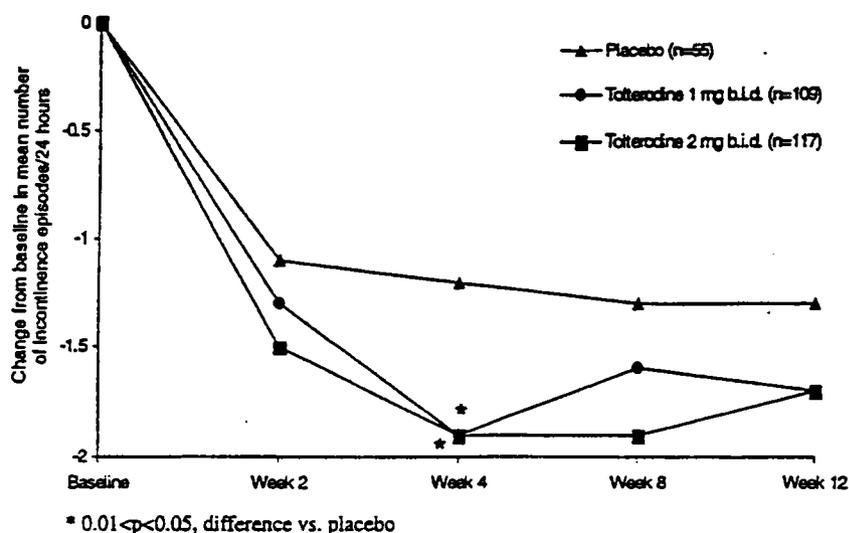
The results of the statistical analyses for the mean number of incontinence episodes per 24 hours at baseline and Week 12 are presented in the following table and figure. Patients without incontinence episodes at baseline are not included in the table and figure.

Study 009: Mean Number of Incontinence Episodes per 24 Hours

	Placebo	Tolterodine 1 mg	Tolterodine 2 mg
N (Missing Data)	55 (0)	109 (1)	117 (1)
n (patients without incontinence at baseline)	9	14	12
n (patients who developed incontinence during study)	1	4	6
Baseline			
Mean (SD)	3.5 (3.2)	3.9 (4.0)	3.6 (4.0)
Range			
Week 12			
Mean (SD)	2.2 (3.6)	2.2 (3.1)	1.8 (3.1)
Range			
Chg. From Baseline at Week 12			
Mean (SD)	-1.3 (2.5)	-1.7 (2.8)	-1.7 (2.5)
Range			
Difference from Placebo			
Mean Difference (SEM)		-0.4 (0.3)	-0.4 (0.3)
p (Appropriate Contrast)		0.27	0.19

(Source: Table 20, vol. 1.2)

The following figure provides the results at baseline and Weeks 2, 4, 8, and 12 for the ITT population.



After 12 weeks of treatment, both tolterodine 1 and 2 mg bid reduced the mean number of incontinence episodes per 24 hours from baseline, but the difference in reduction was not statistically significant for either concentration of tolterodine compared with placebo.

Mean Volume Voided per Micturition (ml)

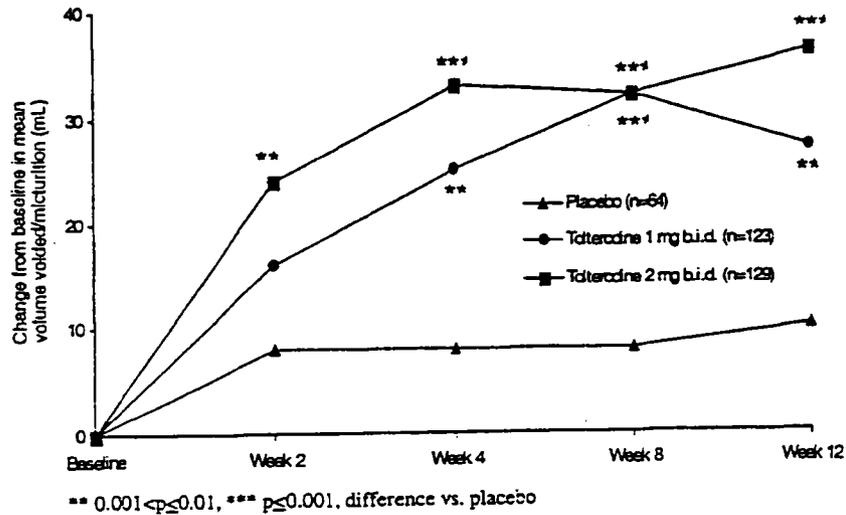
The results of the statistical analyses for the mean volume voided per micturition (ml) per 24 hours at baseline and Week 12 are presented in the following table and figure.

Study 009: Mean Volume Voided per Micturition

	Placebo	Tolterodine 1 mg	Tolterodine 2 mg
N (Missing Data)	64 (0)	123 (0)	129 (1)
Baseline Mean (SD) Range	158 (53)	151 (56)	155 (52)
Week 12 Mean (SD) Range	168 (63)	178 (69)	190 (70)
Chg. From Baseline at Week 12 Mean (SD) Range	10 (47)	27 (41)	36 (50)
Difference from Placebo Mean Difference (SEM) p (Appropriate Contrast)		17 (6) 0.0059	26 (6) 0.0001

(Source: Table 23, vol. 1.2)

The following figure provides the results at baseline and Weeks 2, 4, 8, and 12 for the ITT population.



The difference in increase from baseline after 12 weeks of treatment in the mean volume voided per micturition was statistically significant in favor of both tolterodine 1 mg bid compared with placebo and tolterodine 2 mg bid compared with placebo.

Study 010

In Study 010, 277 patients were randomized to treatment with tolterodine 2 mg bid, oxybutynin 5 mg tid or placebo in the ratio 2:2:1 at 25 centers (15 in USA, 10 in Canada).

Patient Disposition

Patient disposition results for ITT population are given in the following table.

Study 010: Patient Disposition

No. of Patients	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
Randomized	56 (100%)	109 (100%)	112 (100%)
Completed	49 (87.5%)	96 (88.1%)	78 (69.6%)
Withdrawn	7 (12.5%)	13 (11.9%)	34 (30.4%)

(Source: Table 13, vol. 1.2)

Baseline Comparison

The following table provides descriptive statistics for baseline comparison.

Study 010: Baseline Comparison

Variable	Placebo		Tolterodine 2 mg		Oxybutynin	
	N	Mean (Range)	N	Mean (Range)	N	Mean (Range)
BMI (kg/m ²)	56	29.1	109	29.0	112	28.0
Age (yr.)	56	62.1	109	63.0	112	66.3
	n	%	n	%	n	%
Gender						
Male	11	19.6%	21	19.3%	31	27.7%
Female	45	80.4%	88	80.7%	81	72.3%
Race						
Caucasian	52	92.9%	95	87.2%	105	93.8%
Non-Caucasian	4	7.1%	14	12.8%	7	6.2%

(Source: Table 14, vol. 1.2)

Mean BMI (Body Mass Index) and mean age were similar across the treatment groups. There was a greater percentage of females compared with males and Caucasians compared with Non-Caucasians.

Efficacy Analysis

Mean Number of Micturitions per 24 Hours

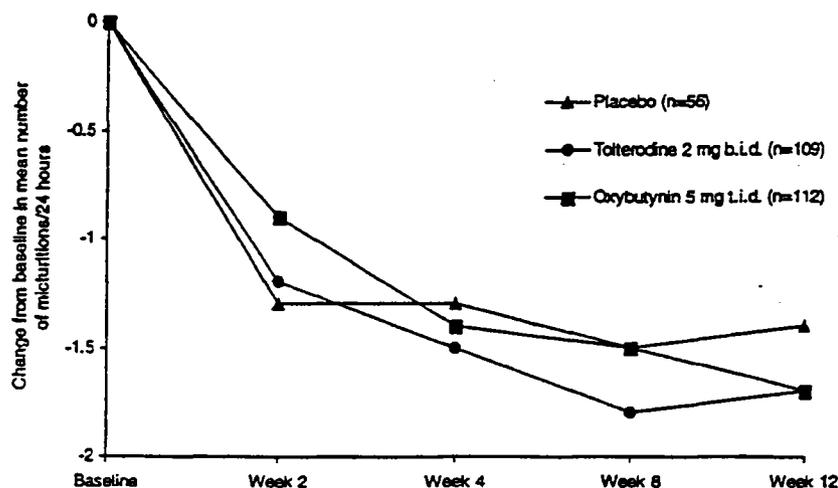
The results of the statistical analyses for the mean number of micturitions per 24 hours at baseline and Week 12 are presented in the following table and figure.

Study 010: Mean Number of Micturitions per 24 Hours

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	56 (0)	108 (1)	112 (0)
Baseline			
Mean (SD)	11.6 (3.1)	11.6 (2.9)	11.5 (3.5)
Range			
Week 12			
Mean (SD)	10.2 (3.1)	9.9 (2.9)	9.8 (3.5)
Range			
Chg. From Baseline at Week 12			
Mean (SD)	-1.4 (2.8)	-1.7 (2.3)	-1.7 (3.0)
Range			
Difference from Placebo			
Mean Difference (SEM)		-0.38 (0.34)	-0.36 (0.34)
p (Appropriate Contrast)		0.27	0.29

(Source: Table 18, vol. 1.2)

The following figure provides the results at baseline and Weeks 2, 4, 8, and 12 for the ITT population.



The difference in reduction from baseline after 12 weeks of treatment in the mean number of micturitions per 24 hours was not statistically significant in favor of tolterodine 2 mg bid compared with placebo.

Mean Number of Incontinence Episodes per 24 Hours

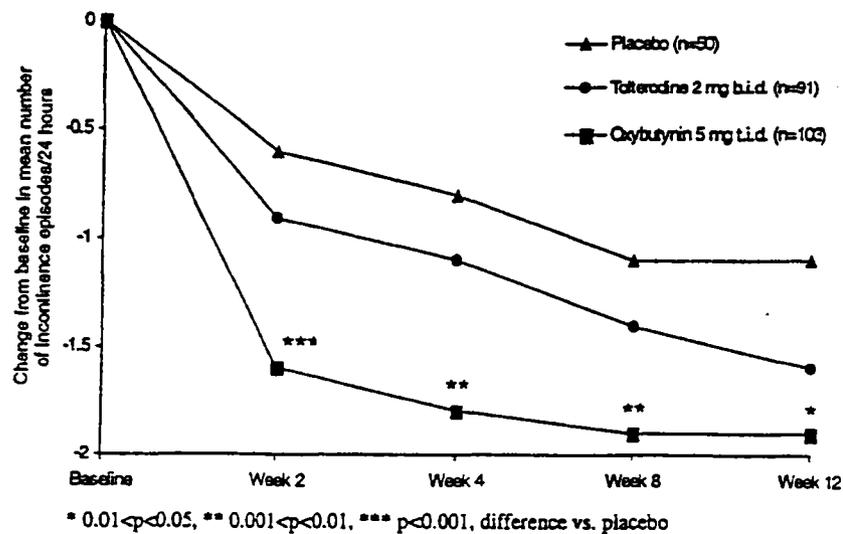
The results of the statistical analyses for the mean number of incontinence episodes per 24 hours at baseline and Week 12 are presented in the following table and figure. Patients without incontinence episodes at baseline are not included in the table and figure.

Study 010: Mean Number of Incontinence Episodes per 24 Hours

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	50 (0)	90 (1)	103 (0)
n (patients without incontinence episodes at baseline)	6	18	9
n (patients who developed incontinence during study)	2	4	0
Baseline			
Mean (SD)	3.5 (3.3)	3.7 (3.3)	3.4 (3.1)
Range			
Week 12			
Mean (SD)	2.4 (3.0)	2.1 (3.3)	1.5 (2.4)
Range			
Chg. From Baseline at Week 12			
Mean (SD)	-1.1 (2.1)	-1.6 (2.4)	-1.9 (2.3)
Range			
Difference from Placebo			
Mean Difference (SEM)		-0.5 (0.3)	-0.8 (0.3)
p (Appropriate Contrast)		0.13	0.012

(Source: Table 21, vol. 1.2)

The following figure provides the results at baseline and weeks 2, 4, 8, and 12 for the ITT population.



The difference in reduction from baseline after 12 weeks of treatment in the mean number of incontinence episodes per 24 hours was not statistically significant in favor of tolterodine 2 mg bid compared with placebo.

Mean Volume Voided per Micturition (ml)

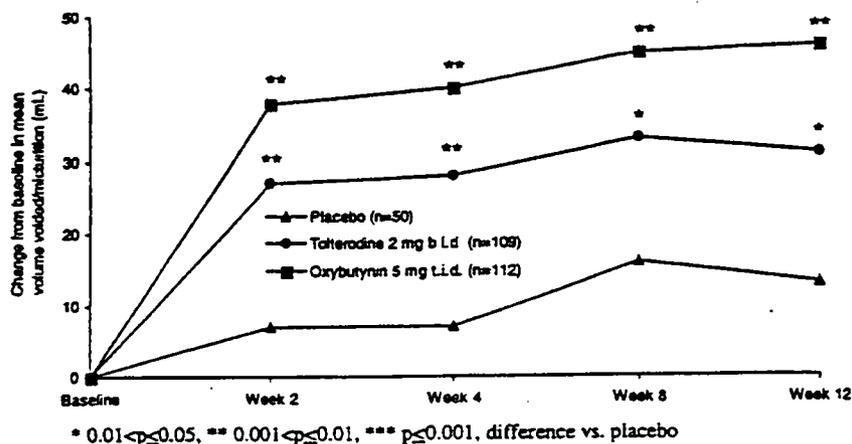
The results of the statistical analyses for the mean volume voided per micturition (ml) per 24 hours at baseline and Week 12 are presented in the following table and figure.

Study 010: Mean Volume Voided per Micturition

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	56 (0)	108 (1)	112 (0)
Baseline			
Mean (SD)	160 (73)	155 (57)	149 (56)
Range			
Week 12			
Mean (SD)	173 (86)	186 (84)	195 (79)
Range			
Chg. From Baseline at Week 12			
Mean (SD)	13 (52)	31 (45)	46 (49)
Range			
Difference from Placebo			
Mean Difference (SEM)		18 (7)	33 (7)
p (Appropriate Contrast)		0.015	0.0001

(Source: Table 24, vol. 1.2)

The following figure provides the results at baseline and Weeks 2, 4, 8, and 12 for the ITT population.



The difference in increase from baseline after 12 weeks of treatment in the mean volume voided per micturition was statistically significant in favor of tolterodine 2 mg bid compared with placebo.

Sponsor's Pooled Analysis for the ITT Population for Studies 008, 009 and 010

The sponsor submitted an analysis of the pooled data for the three studies (008, 009 and 010). For the pooled analyses, patients who reduced their tolterodine dose from 2 mg bid to 1 mg bid are included with patients randomized to 1 mg bid because they had taken 2 mg bid for a maximum of only 2 weeks of the 12-week study. This increased the number of patients on tolterodine 1 mg bid for analysis. All patients who received oxybutynin, including those who reduced their dose, are presented together since the dose reduction varied by country in these multicenter trials.

Mean Number of Micturitions per 24 Hours

The results of the pooled analyses for the mean number of micturitions per 24 hours at baseline and week 12 are presented in the following table for the ITT population. The analyses of the pooled data demonstrate a statistically significant decrease from baseline in the mean number of micturitions per 24 hour with tolterodine 1 and 2 mg bid compared with placebo.

Pooled Analysis: Mean Number of Micturations per 24 Hours

	Placebo	Tolterodine 1 mg	Tolterodine 2 mg	Oxybutynin 5 mg
n (missing data)	176 (1)	140 (0)	337 (2)	229 (1)
Baseline				
Mean (SD)	11.5 (3.8)	11.5 (3.6)	11.5 (3.5)	11.1 (3.4)
Week 12				
Mean (SD)	10.1 (3.4)	9.2 (2.7)	9.2 (2.8)	9.1 (3.2)
Change from Baseline				
Mean (SD)	-1.4 (2.9)	-2.2 (2.9)	-2.3 (2.9)	-2.0 (2.8)
Difference from Placebo				
Mean Diff (SEM)		-0.8 (0.2)	-0.9 (0.2)	-0.6 (0.2)
p-value		0.0008	0.0001	0.0081

(Source: Table 16, Vol. 1.199)

Results for Subgroups (Gender, Race and Age)

Age:

In patients younger than 65 years of age, a statistically significant decrease in the mean number of micturations per 24 hours was observed after 12 weeks of treatment in the tolterodine 1 mg and 2 mg bid groups as compared with the placebo group (see Table 1 in the Appendix).

Gender:

In male and female patients, a statistically significant decrease in the mean number of micturations per 24 hours was observed after 12 weeks of treatment in the tolterodine 1 mg and 2 mg bid groups compared with the placebo group (see Table 2 in the Appendix).

Race:

In Caucasian patients, a statistically significant decrease in the mean number of micturations per 24 hours was observed after 12 weeks of treatment in the tolterodine 1 mg and 2 mg bid groups compared with the placebo group (see Table 3 in the Appendix).

Mean Number of Incontinence Episodes per 24 Hours

The results of the pooled analyses for the mean number of incontinence episodes per 24 hours at baseline and week 12 are presented in the following table for the ITT population.

Pooled Analysis: Mean Number of Incontinence Episodes per 24 Hours

	Placebo	Tolterodine 1 mg	Tolterodine 2 mg	Oxybutynin 5 mg
n (missing data)	145 (2)	120 (0)	287 (3)	191 (2)
n (patients without incontinence at baseline)	30	19	49	37
n (patients who developed incontinence during study)	6	4	16	5
Baseline				
Mean (SD)	3.4 (3.4)	3.8 (3.8)	3.4 (3.6)	3.0 (3.2)
Week 12				
Mean (SD)	2.3 (3.5)	2.1 (3.0)	1.9 (3.0)	1.2 (2.0)
Change from Baseline				
Mean (SD)	-1.1 (2.1)	-1.7 (2.7)	-1.6 (2.7)	-1.8 (2.7)
Difference from Placebo				
Mean Diff (SEM)		-0.5 (0.2)	-0.5 (0.2)	-0.7 (0.2)
p-value		0.023	0.022	0.0011

(Source: Table 23, vol. 1.199)

The analyses of the pooled data demonstrate a statistically significant decrease from baseline in the mean number of incontinence episodes per 24 hour with tolterodine 1 and 2 mg bid compared with placebo.

Results for Subgroups (Gender, Race and Age)

Age:

In patients in both age categories, decreases of similar magnitude was observed in the mean number of incontinence episodes per 24 hours after 12 weeks of treatment with tolterodine 1 mg and 2 mg bid (see Table 4 in the Appendix).

Gender:

In female patients, a statistically significant decrease in the mean number of micturitions per 24 hours was observed after 12 weeks of treatment in the tolterodine 1 mg and 2 mg bid groups compared with the placebo group (see Table 5 in the Appendix). Although the number of males was too small to make definitive conclusions, the response in male patients paralleled that of female patients.

Race:

In Caucasian patients, decreases of similar magnitude in the mean number of incontinence episodes per 24 hours were observed after 12 weeks of treatment in the tolterodine 1 mg and 2 mg bid groups compared with the placebo group (see Table 6 in the Appendix). Although the number of non-Caucasian patients was too

Race:

In Caucasian and non-Caucasian patients, a statistically significant increase in the mean volume voided was observed after 12 weeks of treatment in the tolterodine 1 mg and 2 mg bid groups compared with the placebo group (see Table 9 in the Appendix).

***Statistical Reviewer's Comments on Sponsor's Results for Three Studies
(Based on Sponsor's Parametric Analysis)***

1. Oxybutynin arm in the Study 008 is a *problematic arm* as the sponsor observed a non-significant difference between oxybutynin 5 mg (an approved drug) and placebo for mean number of micturitions per 24 hours. Further, for mean volume voided per micturition, there is a significant difference between oxybutynin 5 mg and tolterodine 2 mg favoring oxybutynin 5 mg. If we "drop" the oxybutynin arm from the study, we may be able to salvage this study. In that case, this study significantly favors tolterodine 2 mg over placebo for the mean number of micturitions per 24 hours and for the mean volume voided per micturition.
2. Study 009 significantly favors tolterodine 1 mg and 2 mg doses over placebo for mean number of micturitions per 24 hours and for mean volume voided per micturition. But, for the mean number of incontinence episodes per 24 hours, this study failed to show any significant differences between tolterodine 1 mg and placebo or between tolterodine 2 mg and placebo.
3. Oxybutynin arm in the Study 010 is a *problematic arm* as the sponsor observed a non-significant difference between oxybutynin 5 mg (an approved drug) and placebo for mean number of micturitions per 24 hours. Further, for mean volume voided per micturition, there is a significant difference between oxybutynin 5 mg and tolterodine 2 mg favoring oxybutynin 5 mg. If we "drop" the oxybutynin arm from the study, we may be able to salvage this study. In that case, this study significantly favors tolterodine 2 mg over placebo for the mean volume voided per micturition.
4. The sponsor's pooled analysis need to be stratified by study. However, for the subgroup of patients that was considered by the sponsor for mean number of incontinence episodes per 24 hours, sponsor's pooled analysis favors tolterodine over placebo.

***Statistical Reviewer's Comments on Sponsor's Results for The Fourth Study
(Based on Sponsor's Parametric Analysis)***

Study 015

The primary aim of this study was to compare the clinical efficacy of tolterodine 2 mg and oxybutynin 5 mg (test for equivalence) after 12 weeks of treatment. The 95% confidence interval for equivalence was defined (in the protocol, page 8/62/163, vol. 259) as (-1.5, 1.5) for the difference between tolterodine and oxybutynin for the two important efficacy variables (mean number of micturations, and mean number of incontinence episodes) without any justification for choosing "-1.5" as the lower confidence limit. There was no discussion or agreement about this with FDA at any point in time.

For the primary efficacy variable of mean number of micturations per 24 hours, the two groups were shown to be weakly equivalent (by the sponsor's definition) for ITT population retaining an outlier in oxybutynin group (patient number . After excluding this patient, equivalence could not be demonstrated.

For mean number of incontinence episodes, the two groups were shown to be equivalent (by the sponsor's definition) for ITT population.

For mean volume voided per micturition, the two groups were not shown to be equivalent (by the sponsor's definition) for ITT population. Actually, the increase in mean volume voided per micturition from baseline to week 12 was significantly greater in the oxybutynin group than in the tolterodine group ($p=0.0032$).

Statistical Reviewer's Conclusions

Tolterodine 2 mg dose is significantly better than placebo for the mean number of micturations per 24 hours (in studies 008 and 009) and for the volume voided per micturition (in studies 008, 009 and 010). All three studies failed to show any significant difference between tolterodine 2 mg and placebo for the mean number of incontinence episodes per 24 hours. In study 009, tolterodine 1 mg dose was statistically significantly favored over placebo for mean number of micturations per 24 hours as well as for mean volume voided per micturition.

III. Statistical Reviewer's Analysis

This reviewer utilized a nonparametric approach to analyze the data as this approach requires less stringent assumptions (as compared to parametric approach) about the data.

Study 008

Number of Micturitions per 24 Hours

The results of the nonparametric statistical analyses for the number of micturitions per 24 hours at baseline and Week 12 are presented in the following table.

Study 008: Number of Micturitions per 24 Hours

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	56 (1)	118 (0)	117 (1)
Baseline Median	10.64	10.50	9.71
Week 12 Median	8.86	8.14	7.75
Chg. From Baseline at Week 12 Median	-1.07	-2.23	-2.14
Difference from Placebo Median Difference p (ANOVA on ranks)		-1.12 0.0036	-1.00 0.0077

Number of Incontinence Episodes per 24 Hours

The results of the nonparametric statistical analyses for the number of incontinence episodes per 24 hours at baseline and Week 12 are presented in the following table. Patients without incontinence episodes at baseline are not included in the following table.

Study 008: Number of Incontinence Episodes per 24 Hours

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	40 (2)	93 (1)	88 (2)
n (patients without incontinence at baseline)	15	24	28
n (patients who developed incontinence during study)	3	6	5
Baseline Median	2.46	2.43	2.00
Week 12 Median	1.00	0.57	0.14
Chg. From Baseline at Week 12 Median	-0.79	-1.21	-1.29
Difference from Placebo Median Difference p (ANOVA on ranks)		-0.43 0.0988	-0.55 0.0401

Volume Voided per Micturition (ml)

The results of the nonparametric statistical analyses for the volume voided per micturition at baseline and Week 12 are presented in the following table.

Study 008: Volume Voided per Micturition

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	56 (1)	118 (0)	116 (2)
Baseline Median	155.4	156.1	168.9
Week 12 Median	159.2	198.6	212.0
Chg. From Baseline at Week 12 Median	5.2	34.0	45.5
Difference from Placebo Median Difference p (ANOVA on ranks)		28.2 0.0001	40.4 0.0001

Study 009

Number of Micturitions per 24 Hours

The results of the nonparametric statistical analyses for the number of micturitions per 24 hours at baseline and Week 12 are presented in the following table.

Study 009: Number of Micturitions per 24 Hours

	Placebo	Tolterodine 1 mg	Tolterodine 2 mg
N (Missing Data)	64 (0)	123 (0)	128 (2)
Baseline Median	10.38	10.43	10.41
Week 12 Median	9.29	9.00	8.29
Chg. From Baseline at Week 12 Median	-1.21	-1.96	-2.18
Difference from Placebo Median Difference p (ANOVA on ranks)		-0.71 0.0203	-0.98 0.0027

Number of Incontinence Episodes per 24 Hours

The results of the nonparametric statistical analyses for the number of incontinence episodes per 24 hours at baseline and Week 12 are presented in the following table.

Study 009: Number of Incontinence Episodes per 24 Hours

	Placebo	Tolterodine 1 mg	Tolterodine 2 mg
N (Missing Data)	55 (0)	108 (2)	116 (2)
n (patients without incontinence at baseline)	9	14	12
n (patients who developed incontinence during study)	1	4	6
Baseline Median	3.17	3.00	2.50
Week 12 Median	1.14	0.86	0.57
Chg. From Baseline at Week 12 Median	-1.14	-1.50	-1.43
Difference from Placebo Median p (ANOVA on ranks)		-0.29 0.3156	-0.32 0.2382

Patients without incontinence episodes at baseline are not included in the above table.

Study 010: Number of Incontinence Episodes per 24 Hours

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	50 (0)	90 (1)	103 (0)
n (patients without incontinence at baseline)	6	18	9
n (patients who developed incontinence during study)	2	4	0
Baseline Median	2.23	2.69	2.57
Week 12 Median	1.31	0.76	0.71
Chg. From Baseline at Week 12 Median	-0.93	-1.48	-1.50
Difference from Placebo Median p (ANOVA on ranks)		-0.57 0.0557	-0.57 0.0531

Volume Voided per Micturition (ml)

The results of the nonparametric statistical analyses for the volume voided per micturition at baseline and Week 12 are presented in the following table.

Study 010: Volume Voided per Micturition

	Placebo	Tolterodine 2 mg	Oxybutynin 5 mg
N (Missing Data)	56 (0)	108 (1)	112 (0)
Baseline Median	164.2	148.0	142.7
Week 12 Median	164.5	172.4	195.6
Chg. From Baseline at Week 12 Median	9.7	27.3	40.7
Difference from Placebo Median Difference p (ANOVA on ranks)		17.1 0.0085	30.0 0.0001

**Statistical Reviewer's Comments about the Three Studies
(Based on Nonparametric Analysis)**

1. The primary objective of the Study 008 was to compare tolterodine 2 mg bid with placebo (test for difference) and oxybutynin 5 mg tid (test for equivalence) after 12 weeks of treatment in patients with detrusor instability and symptoms of frequency and either urge incontinence or urgency, or both.

This study significantly favors tolterodine 2 mg over placebo for the number of micturitions per 24 hours and for the volume voided per micturition.

For the number of incontinence episodes per 24 hours, there is a significant difference between oxybutynin 5 mg and placebo whereas there is no significant difference between tolterodine 2 mg and placebo. Further, for the volume voided per micturition, there is a significant difference between oxybutynin 5 mg and tolterodine 2 mg favoring oxybutynin 5 mg.

2. Study 009 significantly favors tolterodine 1 mg and 2 mg doses over placebo for the number of micturitions per 24 hours and for volume voided per micturition. But, for the number of incontinence episodes per 24 hours, this study failed to show any significant differences between tolterodine 1 mg and placebo or between tolterodine 2 mg and placebo.
3. Oxybutynin arm in the Study 010 is a *problematic arm* as this reviewer observed a non-significant difference between oxybutynin 5 mg (approved drug) and placebo for number of micturitions per 24 hours. Further, for volume voided per micturition, there is a significant difference between oxybutynin 5 mg and tolterodine 2 mg favoring oxybutynin 5 mg. If we "drop" the oxybutynin 5 mg arm from the study, we may be able to salvage this study. In that case, this study significantly favors tolterodine 2 mg over placebo for the volume voided per micturition.

***Statistical Reviewer's Conclusions
(Based on Nonparametric Analysis)***

Tolterodine 2 mg dose is significantly better than placebo for the number of micturitions per 24 hours (in studies 008 and 009) and for the volume voided per micturition (in studies 008, 009 and 010). All the three studies failed to show any significant difference between tolterodine 2 mg and placebo for the number of incontinence episodes per 24 hours. In Study 009, tolterodine 1 mg dose was statistically significantly favored over placebo for the number of micturitions per 24 hours as well as for the volume voided per micturition.

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IV. Statistical Reviewer's Conclusions That May Be Conveyed To The Sponsor

The sponsor has submitted the results of four studies (008, 009, 010 and 015) as proof of the effectiveness and safety of tolterodine 2 mg bid for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. The data from Study 015 (an active-controlled study to show equivalence with oxybutynin) does not support the equivalence of tolterodine 2 mg bid with oxybutynin 5 mg tid for all the efficacy variables.

Tolterodine 2 mg dose is significantly better than placebo for the number of micturitions per 24 hours (in studies 008 and 009) and for the volume voided per micturition (in studies 008, 009 and 010). All the three studies failed to show any significant difference between tolterodine 2 mg and placebo for the number of incontinence episodes per 24 hours. In Study 009, tolterodine 1 mg dose was statistically significantly favored over placebo for the number of micturitions per 24 hours as well as for the volume voided per micturition.

JSI

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Concur: Dr. Kammerman

3/6/98

Dr. Nevius

3/6/98

cc: Archival NDA 20-771
HFD-580/Rarick, Shames, Dunson
HFD-715/Nevius, Kammerman, Taneja, Division File

This review contains 34 pages: 25 pages of text and 9 pages of Tables.

Appendix

Table 1

**Table 17. Efficacy Results by Age Group, Mean Number of Micturations per 24 Hours:
Pooled Data (Studies 008, 009, and 010), Intent-to-Treat Population**

Age category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Age <65				
n (missing data)	94 (1)	81 (0)	198 (1)	111 (1)
Baseline				
Mean (SD)	11.6 (4.2)	11.7 (3.9)	11.7 (3.9)	11.3 (3.9)
Week 12				
Mean (SD)	9.8 (3.4)	9.0 (3.0)	9.0 (2.7)	8.7 (2.9)
Change from baseline				
Mean (SD)	-1.8 (3.2)	-2.8 (3.1)	-2.7 (3.3)	-2.6 (3.3)
Difference from placebo				
Mean difference (SEM)	NAP ^d	-1.0 (0.5)	-0.9 (0.4)	-0.8 (0.5)
p-value vs placebo ^e	NAP	0.043	0.020	0.077
Age ≥ 65				
n (missing data)	82 (0)	59 (0)	139 (1)	118 (0)
Baseline				
Mean (SD)	11.5 (3.4)	11.1 (3.2)	11.1 (3.0)	11.0 (3.0)
Week 12				
Mean (SD)	10.4 (3.3)	9.5 (2.2)	9.5 (2.9)	9.5 (3.5)
Change from baseline				
Mean (SD)	-1.0 (2.5)	-1.6 (2.5)	-1.7 (2.1)	-1.5 (2.3)
Difference from placebo				
Mean difference (SEM)	NAP	-0.5 (0.4)	-0.6 (0.3)	-0.4 (0.3)
p-value vs placebo ^e	NAP	0.19	0.042	0.18

Source: ISE, Appendix F.1.2.

NAP = Not applicable.

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Appendix

Table 2

**Table 18. Efficacy Results by Gender, Mean Number of Micturitions per 24 Hours:
Pooled Data (Studies 008, 009, and 010), Intent-to-Treat Population**

Gender category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Male				
n (missing data)	46 (1)	29 (0)	75 (1)	61 (0)
Baseline				
Mean (SD)	11.6 (2.9)	11.6 (4.0)	11.0 (2.8)	12.3 (3.9)
Week 12				
Mean (SD)	10.7 (3.3)	9.6 (2.4)	9.0 (2.9)	10.4 (3.6)
Change from baseline				
Mean (SD)	-0.90 (2.35)	-2.06 (3.20)	-1.97 (2.15)	-1.89 (2.90)
Difference from placebo				
Mean difference (SEM)	NAP ^d	-1.16 (0.48)	-1.07 (0.38)	-0.98 (0.40)
p-value vs placebo ^e	NAP	0.017	0.006	0.014
Female				
n (missing data)	130 (0)	111 (0)	262 (1)	168 (1)
Baseline				
Mean (SD)	11.5 (4.1)	11.4 (3.6)	11.6 (3.7)	10.7 (3.2)
Week 12				
Mean (SD)	9.9 (3.4)	9.1 (2.7)	9.2 (2.8)	8.6 (2.9)
Change from baseline				
Mean (SD)	-1.61 (3.06)	-2.29 (2.83)	-2.37 (3.05)	-2.04 (2.83)
Difference from placebo				
Mean difference (SEM)	NAP	-0.69 (0.29)	-0.76 (0.24)	-0.43 (0.26)
p-value vs placebo ^e	NAP	0.016	0.001	0.093

Source: ISE, Appendix F.1.3.

NAP = Not applicable.

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Appendix

Table 3

**Table 19. Efficacy Results by Race, Mean Number of Micturations per 24 Hours:
Pooled Data (Studies 008, 009, and 010), Intent-to-Treat Population**

Race category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Caucasian				
n (missing data)	166 (1)	132 (0)	321 (2)	221 (1)
Baseline				
Mean (SD)	11.5 (3.9)	11.4 (3.6)	11.5 (3.6)	11.1 (3.4)
Week 12				
Mean (SD)	10.2 (3.4)	9.3 (2.7)	9.2 (2.8)	9.0 (3.0)
Change from baseline				
Mean (SD)	-1.4 (2.9)	-2.1 (2.8)	-2.3 (2.9)	-2.1 (2.8)
Difference from placebo				
Mean difference (SEM)	NAP ^d	-0.8 (0.3)	-0.9 (0.3)	-0.7 (0.3)
p-value vs placebo ^e	NAP	0.024	0.001	0.019
Other				
n (missing data)	10 (0)	8 (0)	16 (0)	8 (0)
Baseline				
Mean (SD)	11.0 (2.7)	12.0 (4.9)	11.5 (2.8)	12.1 (3.7)
Week 12				
Mean (SD)	9.0 (2.4)	8.1 (2.8)	9.3 (3.0)	12.2 (6.1)
Change from baseline				
Mean (SD)	-2.0 (1.9)	-3.9 (4.6)	-2.2 (2.2)	0.2 (3.5)
Difference from placebo				
Mean difference (SEM)	NAP	-1.9 (1.4)	-0.2 (1.2)	2.2 (1.4)
p-value vs placebo ^e	NAP	0.18	0.86	0.13

Source: ISE, Appendix F.1.4.

NAP = Not applicable.

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Appendix

Table 4

**Table 27. Efficacy Results by Age Group, Mean Number of Incontinence Episodes per 24 Hours:
(Patients Without Incontinence Episodes at Baseline Removed from Analysis) Pooled Data
(Studies 008, 009, and 010). Intent-to-Treat Population**

Age category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Age <65				
n (missing data)	76 (2)	70 (0)	170 (2)	86 (2)
n (patients without incontinence at baseline)	17	11	27	24
Baseline				
Mean (SD)	3.3 (3.5)	4.1 (4.7)	3.5 (3.9)	3.1 (3.7)
Week 12				
Mean (SD)	2.1 (3.4)	2.2 (3.0)	1.7 (2.8)	0.9 (1.6)
Change from baseline				
Mean (SD)	-1.1 (2.1)	-1.9 (2.9)	-1.7 (3.1)	-2.2 (3.4)
Difference from placebo				
Mean difference (SEM)	NAP ^d	-0.8 (0.5)	-0.6 (0.4)	-1.0 (0.5)
p-value vs placebo ^e	NAP	0.10	0.14	0.026
Age ≥ 65				
n (missing data)	69 (0)	50 (1)	117 (1)	105 (0)
n (patients without incontinence at baseline)	13	8	22	13
Baseline				
Mean (SD)	3.6 (3.3)	3.3 (2.0)	3.3 (3.1)	3.0 (2.7)
Week 12				
Mean (SD)	2.5 (3.6)	2.0 (3.0)	2.0 (3.3)	1.5 (2.3)
Change from baseline				
Mean (SD)	-1.1 (2.2)	-1.3 (2.4)	-1.3 (2.0)	-1.5 (1.9)
Difference from placebo				
Mean difference (SEM)	NAP	-0.2 (0.4)	-0.2 (0.3)	-0.4 (0.3)
p-value vs placebo ^e	NAP	0.69	0.50	0.21

Source: ISE, Appendix F.2.2.

NAP = Not applicable.

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Appendix

Table 5

**Table 23. Efficacy Results by Gender, Mean Number of Incontinence Episodes per 24 Hours:
(Patients Without Incontinence Episodes at Baseline Removed from Analysis) Pooled Data
(Studies 008, 009, and 010), Intent-to-Treat Population**

Gender category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Male				
n (missing data)	29 (1)	23 (0)	51 (1)	42 (0)
n (patients without incontinence at baseline)	17	6	24	19
Baseline				
Mean (SD)	4.1 (4.4)	2.9 (2.6)	2.3 (2.4)	2.3 (3.0)
Week 12				
Mean (SD)	2.5 (4.8)	1.3 (1.9)	1.4 (2.6)	1.1 (2.2)
Change from baseline				
Mean (SD)	-1.6 (3.3)	-1.6 (1.6)	-0.9 (2.4)	-1.3 (1.7)
Difference from placebo				
Mean difference (SEM)	NAP ^d	-0.1 (0.5)	0.7 (0.4)	0.3 (0.4)
p-value vs placebo ^c	NAP	0.90	0.062	0.45
Female				
n (missing data)	116 (1)	97 (0) ^e	236 (2)	149 (2)
n (patients without incontinence at baseline)	13	13	25	18
Baseline				
Mean (SD)	3.3 (3.1)	4.0 (4.0)	3.7 (3.7)	3.2 (3.2)
Week 12				
Mean (SD)	2.3 (3.1)	2.3 (3.1)	1.9 (3.0)	1.3 (2.0)
Change from baseline				
Mean (SD)	-1.0 (1.8)	-1.7 (2.9)	-1.7 (2.8)	-2.0 (2.9)
Difference from placebo				
Mean difference (SEM)	NAP	-0.7 (0.3)	-0.7 (0.2)	-1.0 (0.2)
p-value vs placebo ^c	NAP	0.016	0.002	0.0001

Source: ISE, Appendix F.2.3.

NAP = Not applicable.

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Appendix

Table 6

**Table 29. Efficacy Results by Race, Mean Number of Incontinence Episodes per 24 Hours
(Patients Without Incontinence Episodes at Baseline Removed from Analysis):
Pooled Data (Studies 008, 009, and 010), Intent-to-Treat Population**

Race category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Caucasian				
n (missing data)	138 (2)	115 (0)	274 (3)	186 (2)
n (patients without incontinence at baseline)	27	16	46	34
Baseline				
Mean (SD)	3.5 (3.5)	3.8 (3.8)	3.4 (3.6)	3.0 (3.2)
Week 12				
Mean (SD)	2.4 (3.6)	2.1 (3.0)	1.9 (3.0)	1.2 (2.1)
Change from baseline				
Mean (SD)	-1.1 (2.2)	-1.6 (2.8)	-1.5 (2.7)	-1.8 (2.7)
Difference from placebo				
Mean difference (SEM)	NAP ^d	-0.5 (0.3)	-0.4 (0.3)	-0.7 (0.3)
p-value vs placebo ^e	NAP	0.12	0.112	0.019
Other				
n (missing data)	7 (0)	5 (0)	13 (0)	5 (0)
n (patients without incontinence at baseline)	3	3	3	3
Baseline				
Mean (SD)	1.6 (0.9)	4.0 (4.8)	3.7 (3.3)	2.8 (3.8)
Week 12				
Mean (SD)	0.4 (0.5)	1.6 (3.0)	1.5 (2.6)	0.5 (0.8)
Change from baseline				
Mean (SD)	-1.1 (0.6)	-2.4 (1.9)	-2.1 (4.1)	-2.2 (4.1)
Difference from placebo				
Mean difference (SEM)	NAP	-1.3 (1.9)	-1.0 (1.5)	-1.1 (1.9)
p-value vs placebo ^e	NAP	0.51	0.53	0.58

Source: ISE, Appendix F.2.4.

NAP = Not applicable.

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Appendix

Table 7

**Table 37. Efficacy Results by Age Group, Mean Volume Voided (ml) per Micturition:
Pooled Data (Studies 008, 009, and 010), Intent-to-Treat Population**

Age category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Age <65				
n (missing data)	94 (1)	81 (0)	198 (1)	110 (2)
Baseline				
Mean (SD)	165.2 (62.1)	146.5 (49.5)	167.0 (60.3)	172.8 (63.3)
Week 12				
Mean (SD)	176.8 (71.8)	179.9 (68.6)	206.3 (83.4)	224.1 (84.7)
Change from baseline				
Mean (SD)	11.7 (51.5)	33.4 (43.3)	39.3 (56.9)	51.3 (57.5)
Difference from placebo				
Mean difference (SEM)	NAP ^d	21.7 (8.2)	27.7 (6.8)	39.7 (7.6)
p-value vs placebo ^c	NAP	0.008	0.0001	0.0001
Age ≥ 65				
n (missing data)	82 (0)	59 (0)	139 (1)	118 (0)
Baseline				
Mean (SD)	151.0 (63.1)	156.7 (58.7)	148.1 (51.6)	155.2 (56.2)
Week 12				
Mean (SD)	158.6 (71.8)	177.9 (63.9)	176.8 (65.0)	194.9 (76.6)
Change from baseline				
Mean (SD)	7.7 (41.3)	21.3 (33.7)	28.7 (38.8)	41.7 (49.4)
Difference from placebo				
Mean difference (SEM)	NAP	13.6 (7.2)	21.0 (5.9)	34.0 (6.0)
p-value vs placebo	NAP	0.060	0.0004	0.0001

Source: ISE, Appendix F.3.2.

NAP = Not applicable.

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Appendix

Table 8

**Table 38. Efficacy Results by Gender, Mean Volume Voided (ml) per Micturition:
Pooled Data (Studies 008, 009, and 010), Intent-to-Treat Population**

Gender category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Male				
n (missing data)	46 (1)	29 (0)	75 (1)	60 (1)
Baseline				
Mean (SD)	146.5 (57.3)	163.8 (63.1)	167.2 (57.5)	156.0 (51.0)
Week 12				
Mean (SD)	155.9 (66.8)	192.9 (73.3)	196.5 (80.8)	194.4 (72.2)
Change from baseline				
Mean (SD)	9.5 (42.8)	29.1 (35.1)	29.3 (48.8)	38.4 (47.7)
Difference from placebo				
Mean difference (SEM)	NAP ^d	19.6 (8.8)	19.8 (6.9)	28.9 (7.2)
p-value vs placebo ^e	NAP	0.026	0.004	0.0001
Female				
n (missing data)	130 (0)	111 (0)	262 (1)	168 (1)
Baseline				
Mean (SEM)	162.8 (64.3)	147.4 (50.6)	156.9 (57.5)	165.0 (63.4)
Week 12				
Mean (SEM)	172.7 (73.7)	175.5 (64.4)	193.4 (76.8)	214.2 (84.5)
Change from baseline				
Mean (SD)	9.9 (48.5)	28.1 (41.1)	36.5 (50.8)	49.2 (55.4)
Difference from placebo				
Mean difference (SEM)	NAP	18.2 (5.8)	26.6 (4.8)	39.2 (5.2)
p-value vs placebo ^e	NAP	0.0016	0.0001	0.0001

Source: ISE, Appendix F.3.3.

NAP = Not applicable.

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Appendix

Table 9

**Table 39. Efficacy Results by Race, Mean Volume Voided (ml) per Micturition:
Pooled Data (Studies 008, 009, and 010), Intent-to-Treat Population**

Race category	Placebo	Tolterodine ^a (1 mg b.i.d.)	Tolterodine (2 mg b.i.d.)	Oxybutynin ^b (5 mg t.i.d.)
Caucasian				
n (missing data)	166 (1)	132 (0)	321 (2)	220 (2)
Baseline				
Mean (SD)	158.4 (63.1)	151.2 (54.5)	159.4 (57.7)	163.4 (61.0)
Week 12				
Mean (SD)	169.8 (72.5)	177.8 (66.6)	194.0 (75.9)	209.8 (81.9)
Change from baseline				
Mean (SD)	11.4 (47.1)	26.6 (39.6)	34.6 (49.5)	46.4 (52.9)
Difference from placebo				
Mean difference (SEM)	NAP ^d	15.2 (5.7)	23.2 (4.6)	35.0 (5.0)
p-value vs placebo ^e	NAP	0.007	0.0001	0.0001
Other				
n (missing data)	10 (0)	8 (0)	16 (0)	8 (0)
Baseline				
Mean (SD)	160.9 (61.2)	144.2 (36.3)	154.3 (57.0)	142.6 (37.0)
Week 12				
Mean (SD)	144.8 (66.4)	200.6 (64.7)	196.6 (109.1)	187.2 (79.4)
Change from baseline				
Mean (SD)	-16.1 (36.5)	56.4 (34.1)	42.3 (68.0)	44.6 (74.0)
Difference from placebo				
Mean difference (SEM)	NAP	72.6 (27.5)	58.4 (23.4)	60.7 (27.5)
p-value vs placebo ^e	NAP	0.012	0.017	0.033

Source: ISE, Appendix F.3.4.

NAP = Not applicable.

APPEARS THIS WAY
ON ORIGINAL