

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 22-103

Drug Name: Trospium chloride 60 mg extended release capsule

Indication(s): Treatment of Overactive Bladder.

Applicant: Indevus Pharmaceuticals, Inc.

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Table of Contents

1.0 EXECUTIVE SUMMARY..... 3

1.1 Conclusion and Recommendations.....3

1.2 Brief Overview of Clinical Studies.....3

1.3 Statistical Issues and Principal Findings.....4

2.0 INTRODUCTION 5

2.1 Overview5

2.2 Data Sources5

2.3 Indication5

3.0 STATISTICAL EVALUATION..... 6

3.1 EVALUATION OF EFFICACY.....6

3.1.1 Overview of Study -018 and Study -022.....6

3.1.2 Reviewer’s Comments on the Design.....7

3.2 Results: Study -018.....8

3.2.1 Patient Disposition.....8

3.2.2 Patient Demographics and Baseline Characteristics8

3.2.3 Efficacy.....8

3.2.4 Reviewer’s Comment.....11

3.3 Results: Study -022.....11

3.3.1 Patient Disposition.....11

3.3.2 Patient Demographics and Baseline Characteristics11

3.3.3 Efficacy.....12

3.3.4 Reviewer’s Comment.....13

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS13

5.0 SUMMARY AND CONCLUSIONS13

1.0 EXECUTIVE SUMMARY

1.1 Conclusion and Recommendations

Based on the efficacy data submitted from two Phase 3 studies, trospium chloride 60 mg XR demonstrated statistically significant ($p < .001$) improvements (decrease) in average daily toilet voids, average urge urinary incontinence episodes, and increase in volume voided per toilet at week 4 and 12 of treatment, compared to placebo. The improvements were also statistically significant ($p < .05$) at week 1.

From a statistical perspective, this application provided adequate data to support the efficacy of trospium chloride 60 mg XR in the treatment of overactive bladder symptoms.

1.2 Brief Overview of Clinical Studies

The applicant, Indevous Pharmaceuticals, reports efficacy and safety data from two Phase 3 clinical trials (studies -018 and -022) to support trospium chloride 60 mg XR in the treatment of overactive bladder symptoms (OAB). Study -018 was conducted at 55 sites and study -022 was conducted at 66 sites in the United States, respectively. Both studies were parallel-group, randomized, double-blind, double-dummy, placebo-controlled studies, conducted under identical but separate protocol. Patients under OAB therapies were required to undergo a 7-day washout period prior to collection of 3-day baseline urinary diary collection. Eligible patients were randomized on a 1:1 ratio (stratified by the mean baseline number of toilet voids per 24 hours, collected at baseline, using the stratified categories of 10-15, 16-20, and ≥ 21 to ensure fair balance of patient distribution) to receive either trospium chloride 60 mg once daily or placebo during the double-blind treatment period of the study. Treatment outcomes were evaluated at scheduled weeks 1, 4, and 12 of the double-blind Phase of the study. Upon completion of 12-week, if desired, patients could continue to receive trospium chloride 60 mg once daily for another 9 months of open-label Phase of the study.

The protocol-specified efficacy endpoints included two co-primary endpoints: (1) change in average daily toilet voids and, (2) change in average daily urge urinary incontinence (UUI) episodes from baseline to weeks 4, and 12 of the treatment period; and several secondary endpoints such as Volume voided per toilet void, UUI episodes per week, Urgency severity associated with toilet voids (measured by the IUSS instrument), OAB symptom Composite score per day, Urge frequency per day, Stress incontinence episodes frequency per day, Total micturitions (the sum of unique toilet voids and UUI episodes) per day, and Complete responder rate outcome defined as an average of ≤ 8 toilet voids and no UUI episodes per day.

The objective in both the studies was to demonstrate that trospium chloride 60 mg XR is superior to placebo with respect to the two co-primary endpoints. A total of 601 patients in study -018 and a total of 564 patients in study -022, (adjusting for drop outs) were randomized equally to trospium and placebo, respectively.

1.3 Statistical Issues and Principal Findings

The protocols for both studies -018 and -022 were amended to modify the primary efficacy from one endpoint to two co-primary endpoints. Each of the co-primary endpoints was tested at $\alpha=.05$, and therefore, no adjustments for multiplicity were necessary. The sample size was adequate to test both the hypotheses based on the assumed expected effect size and variability. This reviewer did not find any issues that could have impacted the efficacy conclusion other than handling of the missing post-baseline diary data and the statistical analysis method used to handle missing data. In both studies -018 and -022, at week 4 and week 12 of the treatment period, missing diaries were reported by approximately 4% placebo patients, compared to approximately 11% of trospium patients. There appeared to be no pattern in missing, i.e., missing either due to adverse events or lack of efficacy, since patient discontinuations due to AE were similar in both groups. The sponsor's efficacy results using last-observation-carried-forward approach (LOCF) and per protocol (completers at endpoint) analysis population were similar. Based on the applicant's data and confirmed by reviewer's independent analysis, the efficacy results could be summarized as follows:

- (1) In both Phase 3 studies -018 and -022, trospium chloride 60 mg XR demonstrated statistically significant ($p<.001$) improvement (decrease) in both co-primary endpoints: average number of daily toilet voids and average daily urge urinary incontinence episodes at week 4 and 12 of the treatment period, compared to placebo. At week 1, the improvement was also statistically significant ($p<.05$), although, not as pronounced as week 4 and 12.
- (2) Trospium chloride 60 mg XR also demonstrated statistically significant ($p<.001$) increase in the volume voided per toilet starting at week 1 of treatment, and maintained through weeks 4 and 12. Statistically significant ($p<.01$) superiority of trospium 60 mg were also seen with regards to other secondary endpoints evaluated in both studies.

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2.0 INTRODUCTION

2.1 Overview

The applicant, Indevous Pharmaceuticals, is seeking approval of trospium chloride 60 mg extended-release (XR), for the treatment of overactive bladder syndrome (OAB). trospium chloride has been developed as once-daily formulation with dosage strength of 60mg.

To support the safety and efficacy of trospium chloride XR, clinical data from two Phase 3 clinical trials were submitted. In addition, data from two Phase I (PK data to identify optimal formulation), one Phase II (safety data for the new formulation), and one Phase I fast/fed study (PK data on the potential food effect) were also submitted. This review will focus on the efficacy data from the two Phase 3 trials listed in Table 2.1 below.

Table 2.1 Summary of Pivotal Studies

Study#	Study Site (number)	Study Design	Number Randomized /Study Regimen	Duration of Treatment
IP631-018	U.S. (55)	Multi-center, double-blind, placebo-controlled, Phase 3.	Total Randomized: 601 Placebo: 303 Trospium: 298	12 weeks
IP631-022	U.S. (66)	Multi-center, double-blind, placebo-controlled, Phase 3.	Total Randomized: 564 Placebo: 284 Trospium: 280	12 weeks

2.2 Data Sources

The submission was in hard copy and partially electronic. Submitted data were stored in folder \\Cdsub1\n22103\N 000\2006-10-12\m5\datasets in FDA's Electronic Document Room (EDR). The data quality of the submission was within acceptable limits.

2.3 Indication

Trospium chloride 60mg extended release capsules is indicated for the treatment of overactive bladder



3.0 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Overview of Study -018 and Study -022

In this report, for the sake of simplicity, the two Phase 3 studies will be referred as studies -018 and -022, respectively. Both studies were conducted in the U.S. under separate but identical protocol. Therefore, unless otherwise indicated, the descriptions below are applicable to both studies.

Design and Objectives: Studies -018 and -022 were multi-center, randomized, and placebo-controlled for a duration of 12 weeks of double-blind Phase, followed by 9-month of open-label Phase, and were conducted at 55 and 66 sites in the U.S., respectively.

The objectives of the two Phase 3 studies were to evaluate the efficacy of once daily dosing of trospium chloride 60 mg extended release capsules compared to placebo, in reducing urinary frequency, urge urinary incontinence (UUI), and other related symptoms associated with OAB over a 12-week treatment period.

Patients currently under OAB therapy at the time of enrollment were required to undergo 7-day wash out period, followed by 3-day baseline urinary diary collection, prior to randomization. Patients not under OAB therapy could begin treatment after 3-days of baseline diary collection. Patients were randomized on a 1:1 ratio (stratified by the mean baseline number of toilet voids per 24 hours, collected at baseline, using the stratified categories of 10-15, 16-20, and ≥ 21 to ensure fair balance of patient distribution) to receive either trospium chloride 60 mg once daily or placebo during the double-blind treatment period of the study. Treatment outcomes were evaluated at scheduled weeks 1, 4, and 12 of the double-blind Phase of the study. Upon completion of 12-week, if desired, patients could continue to receive trospium chloride 60 mg once daily for another 9 months of open-label Phase of the study.

Efficacy Endpoints: As per protocol, the following two endpoints were considered co-primary:

- 1) Change (from baseline to weeks 4, and 12 of treatment period) in average number of toilet voids (frequency) per 24 hours
- 2) Change (from baseline to weeks 4, and 12 of treatment period) in average urge urinary incontinence (UUI) episodes per day.

Secondary Efficacy Endpoints: The following variables were evaluated as secondary endpoints in both studies -018 and -022:

- 1) UUI episodes per week
- 2) Urgency severity associated with toilet voids (measured by the IUSS instrument)
- 3) OAB symptom Composite score per day
- 4) Volume voided per toilet void
- 5) Urge frequency per day
- 6) Stress incontinence episodes frequency per day

- 7) Total micturations (the sum of unique toilet voids and UUI episodes) per day
- 8) Complete responder rate outcome defined as an average of ≤ 8 toilet voids and no UUI episodes per day

Sample Size: The sample size for these studies was calculated to test the superiority hypothesis for both the co-primary endpoints. Using a mean change in the number of toilet voids per 24 hours (from baseline to 12 weeks of treatment) of -1.53 for placebo and -2.51 for trospium chloride 60 mg with a common standard deviation of 2.65 (based on previous Indevous clinical protocols: IP631-003 and IP631-005), a sample size of 155 patients per treatment group was required (to test the null hypothesis using a type-I error rate of .05 and 90% power). For the UUI endpoint, a sample size of 266 patients per treatment group were required, based on a mean change of -1.29 for placebo and -1.71 for trospium chloride, Therefore, adjusting for attrition, a sample size of 300 patients per group was planned in each Phase 3 studies.

Definition of Analysis Population: For efficacy analysis, a patient must have had an average baseline number of events greater than 0 to be included in evaluating the change from baseline. To be included in the weekly analysis, a patient must have 3 toilet voids per day and at least for 3 days of entries. Volume void was collected 2 full days prior to each weekly visit. Therefore, to be included in the weekly analysis, a patient must have 2 days of entries with at least 3 volumes captured per day. The primary and secondary efficacy evaluations were performed using the ITT patient population, defined as all patients who were enrolled and had at least 1 post-baseline diary data.

Analyses were also performed using observed cases (OC) analysis population, defined as data set consists of only the actual data recorded at week 4 and 12.

Statistical Analysis Method: Missing diary data on toilet voids and urge incontinent episodes from the double-blind period of the treatment were imputed by LOCF method from the last available post-baseline diary data. If no data was recorded at weeks 4 and 12, then the data was carried forward from the most recent visit. If no data was recorded at week 1 and there were baseline and analysis week 4 evaluations, then week 1 data was imputed by the average of baseline and week 4 data.

For comparison of treatment groups with respect to both co-primary endpoints, the statistical methods included ANOVA models including center, treatment, and treatment by center interactions as factors. In case of baseline imbalances in outcome variables, an analysis of covariance (ANCOVA) model was used with baseline as factor. If the data was not normally distributed, analyses were performed based on rank transformations of the data and/or median test.

3.1.2 Reviewer's Comments on the Design

The sample size was adequate for testing the superiority hypothesis for both co-primary endpoints in both studies. The statistical analysis method using ANOVA was also appropriate.

3.2 Results: Study -018

3.2.1 Patient Disposition

At 55 sites, a total of 601 patients were randomized approximately equally to the treatment groups as shown in Table 3.2.1. Patient enrollment was similar across sites. No single site was predominant in terms of enrollment. A total of 65 (11%) patients discontinued the study prematurely. The major reasons for discontinuation were adverse event (4%) and withdrawal of consent (3%), followed by lost to follow up (2%). The discontinuation rates were similar across treatment groups, and did not appear to impact the efficacy results. The final ITT analysis (ITT-LOCF) population included 582 patients. A total of 9 patients (3 in placebo and 6 in trospium group) were excluded for no baseline and/or post-baseline diary data).

Table 3.2.1 Disposition of Patients: Study -018

	Placebo N (%)	Trospium N (%)	Total N (%)
Randomized	303	298	601
Reasons for Discontinuation:	30(10.0)	35(11.7)	65(11.0)
Adverse Event	11 (3.6)	12 (4.0)	23 (3.8)
Withdrawn Consent	10 (3.3)	9 (3.0)	19 (3.2)
Protocol deviation	0	2 (0.7)	2 (0.3)
Non-compliance	0	3 (1.0)	3 (0.5)
Lost to follow-up	5 (1.7)	8 (2.7)	13 (2.2)
Other Reasons	4 (1.3)	1 (0.3)	5 (0.8)
Exclusion from Analysis:			
No baseline/post-baseline data	3 (1%)	6 (2%)	9 (1.5%)
ITT Analysis population	300 (99%)	282 (95%)	582 (97%)

3.2.2 Patient Demographics and Baseline Characteristics

The treatment groups were well balanced with regards to demographic and baseline characteristics such as age, race, gender, etc. The majority of the patients were female (85%) and white (86%) and appeared to be representative of the patient population for OAB.

3.2.3 Efficacy

Primary Efficacy: Two co-primary endpoints were evaluated in study -018: Change in average daily toilet voids, and change in average UUI episodes. To evaluate the treatment difference between trospium chloride 60 mg and placebo, we performed statistical analyses similar to sponsor's analysis method using analysis of variance (ANOVA) with center, treatment and center by treatment

interaction term in the model. We also examined the data for normality, and if violated, analysis based on non-parametric method was used. Results of our analyses for both co-primary endpoints are shown in Table 3.2.3.

Change in average daily toilet voids: As shown in Table 3.2.3, starting at week 1 of treatment, the average reductions (improvement) from baseline in the daily number of toilet voids was greater for trospium chloride 60 mg treated patients, compared to placebo patients. The difference in reductions between the two groups were statistically significant ($p < .01$) at week 1, 4, and 12.

Change in average daily Urge Incontinence Episodes: Similar effects were also noted for average reductions in urge incontinence episodes at week 1, 4, and 12. The reductions were again statistically significantly different from placebo after adjusting for multiple comparisons.

Results using completer's (not shown here), similar to the sponsor's definition of observed cases population were similar to ITT using the LOCF analysis population. Both analysis population sets showed consistent efficacy results with respect to both co-primary endpoints in support of trospium chloride 60 mg in treating OAB symptoms.

Secondary Efficacy: Several secondary efficacy endpoints, as noted in section 3.1.1.3, were considered in this study. Among them, the clinical reviewing team considered the changes in the daily voided volume as one of the important secondary endpoint, and, therefore we performed an analysis of voided volume using the same rank ANOVA models. As shown in Table 3.2.3, compared to placebo, trospium chloride 60 mg improved (increased) the mean voided volume from baseline to endpoints. These improvements were statistically significant ($p < .005$) at weeks 1, 4, and 12, compared to placebo.

Summary statistical conclusions of other secondary endpoints are shown in Table 3.2.4. Trospium 60 mg demonstrated statistically significant improvements in these outcomes as well.

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Table 3.2.3 Mean Changes⁺ in Efficacy Endpoints: ITT-LOCF Population, Study -018

Efficacy Endpoints	Week	Trospium N=300	Placebo N=292	Treatment Difference	P-value ⁺⁺
Toilet Voids	Baseline	12.77	12.74	-	
	Change ⁺ :				
	1	-1.65	-1.24	-0.41	0.008
	4	-2.44	-1.58	-0.85	<.0001
UII Episodes/Day	Baseline	4.11	4.14		
	Change ⁺ :				
	1	-1.86	-1.23	0.64	<.0001
	4	-2.36	-1.74	-0.62	0.0013
Volume voided/toilet	Baseline	151.00	156.00		
	Change ⁺ :				
	1	21.90	12.00	9.92	.0038
	4	30.00	17.30	12.72	.0011
	12	29.70	18.90	10.88	.0049

⁺ Change from baseline. ⁺⁺ P-values reported from Rank based ANCOVA model with factors for baseline value, and treatment by center interaction.

Table 3.2.4 Summary of Analyses of Secondary Endpoints:
ITT-LOCF Population, Study -018

Secondary Endpoints	Does Trospium 60 mg demonstrate statistically Significant improvement?	
	Week 4	Week 12
Daily Volume voided	Yes	Yes
UII Episodes/Week	Yes	Yes
Urgency Severity	Yes	Yes
OAB Symptoms (Composite Score)	Yes	Yes
Total Micturations/Day (Toilet voids + UII Episodes)	Yes	Yes

3.2.4 Reviewer's Comment

Results of our independent analysis confirmed the sponsor's conclusion that trospium 60 mg treatment was superior to placebo in the reduction of average number of toilet void and urge incontinence episodes, starting at weeks 1, 4, and 12.

3.3 Results: Study -022

3.3.1 Patient Disposition

At 66 sites, a total of 564 patients were randomized approximately equally to the treatment groups as shown in Table 3.3.1. Patient enrollment was similar across sites. No single site was predominant in terms of patient enrollment. A total of 73 (13%) patients discontinued the study prematurely. The major reasons for discontinuation were adverse event (4%) and lost to follow-up (3%), followed by withdrawal (2%). The discontinuation rates were similar across treatment groups, and did not appear to impact the efficacy results. The final ITT analysis (ITT-LOCF) population included 543 patients. A total of 21 patients were excluded from the analysis population, because of missing baseline and/or post-baseline diary data.

Table 3.3.1 Disposition of Patients: Study -022

	Placebo N (%)	Trospium N (%)	Total N (%)
Randomized	284	280	564
Discontinued:	36(12.7)	37(13.2)	73(13.0)
Adverse Event	8 (2.8)	18 (6.4)	24 (4.2)
Withdrawn Consent	8 (2.8)	7 (2.5)	15 (2.6)
Protocol deviation	2 (0.7)	1(0.4)	3 (0.5)
Non-compliance	1 (0.4)	1 (0.4)	2 (0.3)
Lost to follow-up	10 (3.5)	7 (2.5)	17 (3.0)
Other Reasons	7 (2.5)	3 (1.1)	10 (1.8)
Exclusion from Analysis:			
No baseline/post-baseline data	8 (2.8%)	13 (4.6%)	21 (3.7%)
ITT Analysis population	276 (97%)	267 (95%)	543 (96%)

3.3.2 Patient Demographics and Baseline Characteristics

The baseline characteristics such as age, race, gender, and body mass index were similar across treatment groups. Concomitant medication use and prior drug treatment for OAB were also similar between treatment groups.

3.3.3 Efficacy

Primary Efficacy: Two co-primary endpoints were also evaluated in study -022. We reported average changes from baseline to endpoints and the p-values based on rank ANOVA models for group comparison, since the normality assumptions did not hold for most changes. The center by treatment action term was dropped from the model if p-value was $>.10$.

Change in average daily toilet voids: As shown in Table 3.3.3, starting at week 1 of treatment period, the average reductions (improvement) from baseline in daily toilet voids was greater for trospium chloride 60 mg treated patients, compared to placebo patients. The difference in reductions between the two groups were statistically significant ($p<.01$) at week 1, 4, and 12.

Change in average daily urge incontinence episodes: A similar reductions in urge incontinence episodes were seen at week 1, 4, and 12, when compared to placebo. The average reductions were again statistically significantly ($p<.01$) different from placebo.

Secondary Efficacy: Similar to study -018, trospium chloride 60 mg also improved (increased) the mean voided volume from baseline to endpoints, when compared to placebo, as shown in Table 3.3.3. In addition, analyses of all other supportive secondary endpoints consistently showed statistically significant improvements with trospium chloride 60 mg treatment, as shown in Table 3.2.4.

Table 3.3.3 Mean Changes⁺ in Efficacy Endpoints: ITT-LOCF Population, Study -022

Efficacy Endpoints	Week	Trospium N=267	Placebo N=276	Treatment Difference	P-value ⁺⁺
Toilet Voids	Baseline	12.84	12.94	--	--
	Change ⁺ :				
	1	-1.42	-1.15	-0.27	0.0305
	4	-2.25	-1.71	-0.54	.0013
	12	-2.54	-1.80	-0.74	.0002
UUI Episodes/Day	Baseline	4.02	4.04	--	--
	Change ⁺ :				
	1	-1.73	-1.04	-0.69	<.0001
	4	-2.25	-1.51	-0.79	<.0001
	12	-2.35	-1.62	-0.74	<.0001
Volume voided	Baseline	149.60	151.80		
	Change ⁺ :				
	1	24.00	12.00	9.77	<.0001
	4	29.30	19.60	12.76	.0021
	12	31.50	17.80	10.70	.0011

⁺ Change from baseline. ⁺⁺ P-values reported from Rank based ANCOVA model with factors for baseline value, and treatment by center interaction.

**Table 3.3.4 Summary of Analyses of Secondary Endpoints:
ITT-LOCF Population, Study -022**

Secondary Endpoints	Does trospium 60 mg demonstrate statistically significant improvement?	
	Week 4	Week 12
Daily Volume voided	Yes	Yes
UUI Episodes/Week	Yes	Yes
Urgency Severity	Yes	Yes
OAB Symptoms (Composite Score)	Yes	Yes
Total Micturitions/Day (Toilet voids + UUI Episodes)	Yes	Yes

3.3.4 Reviewer’s Comment

In study -022, the results of our independent analysis confirmed that compared to placebo, trospium chloride 60 mg XR treatment resulted in statistically significant improvements in both co-primary as well as supportive secondary endpoints.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In both studies, co-primary endpoints were also examined by gender, age, and baseline subgroups. In our analysis by gender, there appeared to be no treatment difference in approximately 15% of males, but the number of patients were too small to make a meaningful interpretation. Had the studies enrolled a balanced sample of male and females, probably there could still be treatment differences in favor of trospium in both male and females. Analyses by age and baseline strata of total voids or UUI did not show any meaningful better or worse relative efficacy, although patient with higher baseline values of toilet voids demonstrated a greater numerical decrease when compared with a lower baseline number of toilet voids.

5.0 SUMMARY AND CONCLUSIONS

We have reviewed efficacy data from two Phase 3 studies (studies -018 and -022) in support of trospium chloride 60 mg XR in the treatment of overactive bladder symptoms. Both studies -018 and -022 were similar in design: randomized, placebo-controlled, parallel-group, and conducted under identical but separate protocol in the US.

We performed statistical analyses to evaluate the protocol-specified co-primary and secondary endpoints. Our analysis showed that compared to placebo, trospium chloride 60 mg XR was statistically significantly ($p < .01$) superior in treating OAB, as indicated by the improvements from baseline to weeks 4, and 12 in the two co-primary endpoints: change in average daily toilet voids and average daily urge urinary incontinence episodes; and one key secondary endpoint: change in the voided volume.

From a statistical perspective, the data provided in this application demonstrated the efficacy of trospium chloride 60 mg XR in the treatment of overactive bladder symptoms.

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