

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/BLA Serial Number:** 202513

**Drug Name:** Anturool Gel 3.0%

**Indication(s):** Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency

**Applicant:** Antares Pharma, INC.

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## 1. EXECUTIVE SUMMARY

The data in this application support the efficacy of Anturol 84 mg/day dose for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. <sup>(b) (4)</sup>

This conclusion was based on a single (Study 20070060), double-blind, randomized, multicenter, placebo-controlled 12-week trial with a 24-week open-label extension phase, designed to evaluate the efficacy and safety of topically administered Anturol gel (active ingredient: oxybutynin) in patients with urge and mixed urinary incontinence (UI) with a predominance of urge incontinence episodes.

Three statistical issues were noted in the applicant's analyses of the data in study 20070060:

- The applicant provided two procedures to adjust for multiplicity in this application: one pre-specified prior to data base lock and a modified version after the data base was unblinded. The latter one was in the memo on "clarifying roles of closed testing of two doses versus placebo for primary endpoint and amended strategy for controlling type I error for secondary clinical endpoints", which was submitted in the NDA submission on 12/22/2010. This memo was dated as 08/24/2010 and the analysis results of unblinded data were discussed in it.
- The applicant's statistical method included Mixed Model Repeated Measures (MMRM) analysis based on the rank-transformed data of the efficacy endpoints due to non-normality of the data. This analysis approach, i.e., MMRM based on rank data was neither well understood (or established) in the literature nor in the application. No literature or supported information was submitted by the applicant.
- The applicant's primary analyses were based on the modified ITT population rather than the ITT population for the efficacy endpoints. The modified ITT population defined by the applicant may not represent the potential target population of this test drug.

With regards to the first issue, according to the applicant's submission dated 11/04/2011, the study data was unblinded on 06/21/2010. Therefore, the amendment on the sequence of testing hypotheses in the memo dated 08/24/2010 was after the data unblinding. Any post-hoc change in the hierarchy of testing hypotheses using closed testing procedures is not acceptable, and therefore the statistical review followed the pre-specified procedure in the statistical analysis plan (SAP) dated 06/10/2010. To address the last two issues, the statistical reviewer conducted the efficacy analyses using the rank-ANCOVA model with the ITT population.

The results for the primary efficacy endpoint, i.e., change from baseline to Week 12 in the number of UIE per week, and two secondary endpoints, change from baseline to Week 12 in the average daily urinary frequency and change from baseline to Week 12 in the average urinary void volume per void for study 20070060 are as follows:

- Compared with placebo, Anturol 84 mg/day showed statistically significant reductions in the number of UIE per week and the average daily urinary frequency, and statistically significant increase in the average urinary void volume at Week 12;
- Compared with placebo, the low dose of Anturol 56 mg/day failed to show statistically significant results on the primary and secondary efficacy endpoints at Week 12.

## 2. INTRODUCTION

### 2.1 Overview

This New Drug Application (NDA) was submitted by Antares Pharma INC. to seek approval for Anturol (Oxybutynin gel 3%) as a treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence (UI), urgency and frequency under Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act.

The active ingredient in Anturol is oxybutynin, present in the gel formulation at a concentration of 3%. Oxybutynin (OXY) is a tertiary amine that has anticholinergic and direct spasmolytic effects on the bladder smooth muscle. The currently marketed topical oxybutynin products are Oxytrol® Oxybutynin Transdermal Delivery System (Oxytrol-TDS) and Gelnique® (10% Oxybutynin chloride topical gel) (Watson Pharma, 2006b; Watson Pharma, 2009).

One phase III clinical trial, study 20070060, was submitted in this NDA to demonstrate the safety and efficacy of Anturol gel (at doses of 84 and 56 mg/day) in patients with urge and mixed urinary incontinence with a predominance of urge incontinence episodes. This clinical trial was a 12-week double-blind, randomized, parallel, placebo-controlled, multicenter study with a 24-week open-label extension phase. In the double-blind phase, approximately 600 patients were planned to be randomized to one of the following treatment groups (approximately 200 patients per group):

- Anturol gel 84 mg/day, daily topical application;
- Anturol gel 56 mg/day, daily topical application;
- Matching placebo gel, daily topical application.

After the double-blind phase of the study, a subset of at least 75 of these patients (to ensure 50 patients completed) were planned to participate in a 24 week open-label extension (OLE) to evaluate safety and skin tolerability of Anturol 84 mg/day topically administered over an extended period. The table below summarizes the study design.

Table 1 - List of all studies included in analysis

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
Study 20070060 (Sep. 2007-May 2010 67 sites in US)	double-blind, randomized, multicenter placebo controlled,	Double-blind: 12 weeks	Randomized: 84 mg/day: 214 56 mg/day: 210 placebo : 202	>=18 years old, with OAB symptoms of urge and/or mixed UI with a predominance of urge incontinence >=3 months
	open-label extension	Open-label: 24 weeks	86 patients who had completed the double blind phase rolled over into OLE	

Source: Reviewer's summary based on the study report for 20070060.

The protocol for Study 20070060 was submitted for special protocol assessment in 2006, but no formal agreement was reached between the Division and the Applicant.

### 2.2 Data Sources

The study report and additional information for study 20070060 were submitted electronically. These items are located in the Electronic Document Room at <\\Cdsub1\evsprod\NDA202513> under submission dates 12/22/2010, 03/11/2011, 05/04/2011 and 11/04/2011.

### **3. STATISTICAL EVALUATION**

#### **3.1 Data and Analysis Quality**

A formulation change was made during the course of the study. The clinical data were collected by two contract research organizations and each was only responsible for the data on one formulation. Three sets of clinical data were submitted, one set including all data sets with names ending with “1” for the first formulation, one set including all data sets with names ending with “2” for the second formulation and one set including all data sets with names ending with “3” for combined data.

The submitted SAS data sets for all studies were complete and documented. Minor issues were noted during the review process, i.e. the labels for some variables were truncated in the data sets.

Key tabulation data sets (i.e. raw data) and statistical program to generate the efficacy analysis data set were submitted by the applicant on 05/04/2011 per request by the Division.

#### **3.2 Evaluation of Efficacy**

The evaluation of efficacy of Anturol (oxybutynin gel) was based on the double-blind phase of the Study 20070060.

##### **3.2.1 Study Design and Endpoints**

Study 20070060 was a 12-week double-blind, randomized, multicenter, placebo-controlled trial with a 24-week open-label extension phase, designed to evaluate the efficacy and safety of topically administered Anturol gel (oxybutynin) in patients with urge and mixed urinary incontinence (UI) with a predominance of urge incontinence episodes. Potential study participants who were at least 18 years old, with OAB symptoms for at least 3 months and who were either treatment naïve or had demonstrated a beneficial response to anticholinergic treatment for OAB, were eligible for study entry, provided all other inclusion/exclusion criteria were met. Patients were randomized in a 1:1:1 ratio to three treatment groups, Anturol (84 mg/day), Anturol (56 mg/day) and placebo. Patients were instructed to apply all doses of Anturol or placebo gel at approximately the same time each day during the study. Study drug was applied to the abdomen (stomach area), inner and upper part of the upper thighs, or upper arms/shoulders.

For the double-blind phase of the study, seven study center visits were scheduled: one screening visit (visit 1, week -3); one baseline visit for distribution of 3-day baseline patient urinary diary (visit 2, week -1); one randomization visit (visit 3, week 0); and four double-blind treatment phase visits (visits 4, 5, 6, and 7; weeks 2, 4, 8, and 12). Patient urinary diaries were filled out for week 1, 2, 4, 8 and 12. Patients were reminded to start their urinary diary 5 days after receiving the first dose of study drug for the week 1 diary and 3 days prior to their next scheduled visit for all other diaries and to record urinary void volume on the first 2 days of the 3-day diary.

The primary efficacy endpoint was the change from baseline to Week 12 in the number of UIE per week, as determined from a 3-day patient daily diary. UIE per week was computed as 7 times the mean daily UIE from 3-day urinary diary.

The secondary efficacy endpoints were:

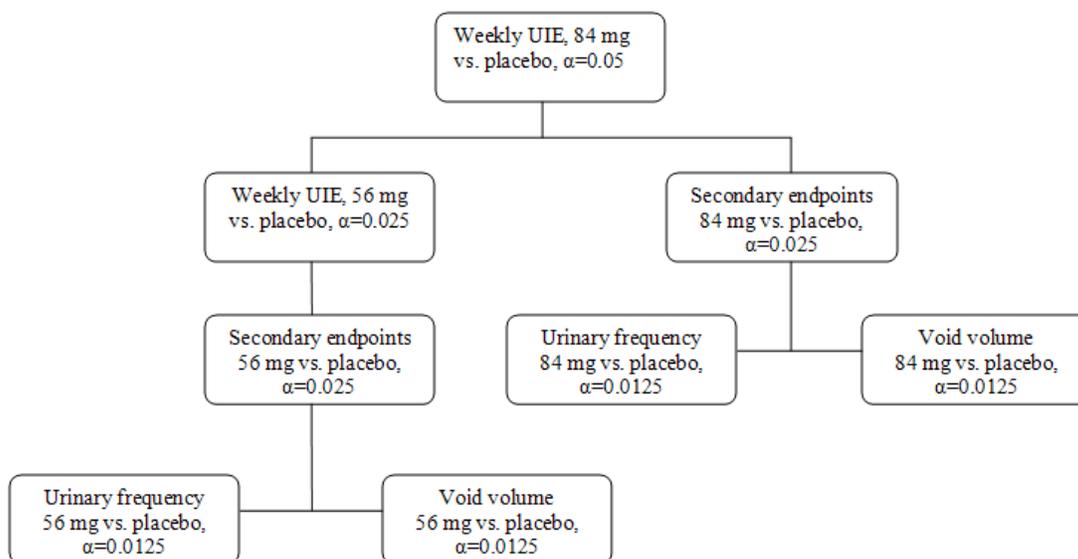
- The change from baseline to Week 12 in the average daily urinary frequency based on the entries in the 3-day patients urinary diary;
- The change from baseline to Week 12 in the average urinary void volume per void based on entries from 2 consecutive days in the 3-day patient’s urinary diary.

A closed testing principle was adopted by the Applicant for testing the primary and secondary endpoints to control the overall type I error, as described below in Figure 1. First, the testing would be conducted between Anturool 84mg/day vs. placebo on the change from baseline in the number of UIE per week. If this test is statistically significant at the 0.05 level (2-sided), then the following 3 tests would be conducted respectively:

- T1. Test between Anturool 56 mg/day vs. placebo on the change from baseline in the number of UIE per week, at the 0.025 level 2-sided;
- T2. Test between Anturool 84 mg/day vs. placebo on the change from baseline in the average daily urinary frequency, at the 0.0125 level 2-sided;
- T3. Test between Anturool 84 mg/day vs. placebo on the change from baseline in the average urinary void volume per void, at the 0.0125 level 2-sided;

If T1 is statistically significant, then tests between Anturool 56 mg/day vs. placebo on the two secondary efficacy endpoints would be conducted respectively at the 0.0125 level (2-sided).

**Figure 1 - Testing sequence for the primary and secondary efficacy endpoints**



Source: Modified from Applicant’s statistical analysis plan (06/10/2010, Version 3, Page 34).  $\alpha$  is the pre-specified level for a 2-sided test.

### 3.2.2 Patient Disposition, Demographic and Baseline Characteristics

#### Patient disposition

Table 2 presents the number of randomized patients and the disposition of the patients. A total of 626 patients were randomized in the study. The early discontinuation rate was 17.3% in Anturol 84 mg group and 21.4% in the 56 mg group, compared to 25.2% in the placebo group. The majority of these premature discontinuations were due to adverse events (AEs), with more patients in the Anturol groups than the placebo group followed by patient decision with more patients in placebo group than Anturol groups.

Table 2 - Randomization and Disposition of All Subjects

	<b>Anturol 84 mg/day</b>	<b>Anturol 56 mg/day</b>	<b>Placebo</b>	<b>All</b>
No. of patients randomized	214 (100.0)	210 (100.0)	202 (100.0)	626 (100.0)
No. of patients completed the study	177 (82.7)	165 (78.6)	151 (74.8)	493 (78.8)
No. of patients rolled over into the OLE	30 (14.0)	31 (14.8)	25 (12.4)	86 (13.7)
No. of patients prematurely discontinued	37 (17.3)	45 (21.4)	51 (25.2)	133 (21.2)
Noncompliance	3 (8.1)	5 (11.1)	1 (2.0)	9 (6.8)
AEs	19 (51.4)	21 (46.7)	10 (19.6)	50 (37.6)
Prohibited concomitant medication	0 (0.0)	1 (2.2)	1 (2.0)	2 (1.5)
Significant protocol deviation	0 (0.0)	2 (4.4)	1 (2.0)	3 (2.3)
Lost to follow-up	2 (5.4)	2 (4.4)	7 (13.7)	11 (8.3)
Patient decision	12 (32.4)	10 (22.2)	25 (49.0)	47 (35.3)
Other	1 (2.7)	4 (8.9)	6 (11.8)	11 (8.3)

Source: Table 5 (Page 60) of the applicant's study report for 20070060.

No.: number; OLE: Open-Label Extension

1. Percentages were calculated (except for reasons for discontinuation) using the number of randomized patients in each treatment group. For reason for discontinuation, percentages were based on the number of discontinued patients in each treatment group.

The intent to treat (ITT) population was defined as the patients who were randomized in the study and received at least one dose of any study drug in the study protocol.

The modified ITT (MITT) population was defined as the patients who were,

- Properly randomized.
- Received at least one dose of study drug.
- Had completed urinary diary on 3 consecutive days at baseline and at least once at post-baseline period.
- Had an average of at least 1 urinary urge episode per day and an average of 8 or more voids per day at baseline.
- Had not used any prohibited prior and/or concomitant medication.

The protocol-specified population for primary analysis of efficacy endpoints is the MITT population.

In Table 3, of 626 randomized patients, 532 patients (85.0%) were included in the MITT population. The main reasons for the exclusion from the MITT Population included protocol violation (49 patients [7.8%]) and study noncompliance (44 patients [7.0%]). Slightly more patients

in the Anturool 56 mg/day and placebo groups were excluded from the MITT population compared with the Anturool 84 mg/day.

Table 3 - Summary of Analysis Populations – All Randomized Patients

	Anturool 84 mg/day	Anturool 56 mg/day	Placebo	All
ITT Population <sup>1</sup>	214 (100.0)	210 (100.0)	202 (100.0)	626 (100.0)
MITT Population <sup>2</sup>	195 (91.1)	171 (81.4)	166 (82.2)	532 (85.0)
Patients Excluded	19 (8.9)	39 (18.6)	36 (17.8)	94 (15.0)
Study Noncompliance	7 (3.3)	19 (9.0)	18 (8.9)	44 (7.0)
Prior and Concomitant Therapy	4 (1.9)	5 (2.4)	3 (1.5)	12 (1.9)
Protocol Violation	11 (5.1)	18 (8.6)	20 (9.9)	49 (7.8)
Secondary Diagnoses and Procedures	2 (0.9)	5 (2.4)	6 (3.0)	13 (2.1)

Source: Table 6 (Page 62) in the applicant's study report for 20070060.

ITT: intent-to-treat; mITT: modified ITT; OLE: Open-Label Extension

1. Intent-to-treat population (primary safety sample) included all randomized patients who received at least one dose of study drug.

2. Modified ITT Population included all ITT patients who met all the MITT population criteria.

## **Demographics and Baseline Characteristics**

Demographic data of all randomized subjects were presented in the Appendix, Table 11. Overall, the mean age of patients was 58.8 years with a range of 19 to 89 years. The majority of the patients were white (542 patients [86.6%]) and female (542 patients [86.6%]). Overall mean (SD) BMI was 31.2 (7.39) Kg/m<sup>2</sup>.

In general, past medical history, physical examination results and other baseline characteristics were similar across treatment groups. The baseline of efficacy endpoints is summarized in the analysis of each efficacy endpoints.

### **3.2.3 Statistical Methods**

#### **3.2.3.1 Applicant's analysis method for primary/secondary efficacy endpoints**

The applicant pre-specified a Mixed Model for Repeated Measures (MMRM) to analyze the mean change from baseline in the number of UIE per week including all patients in the MITT population. The normally-distributed assumption for the response variable in MMRM model was examined. Due to violation of the normality assumption, the applicant sought to normalize the data by log transformation first, and then rank transformation after the log transformation attempt failed to transform the data as normally distributed. The same MMRM model was applied to the rank-transformed UIE data. For primary and secondary endpoints, ranks were determined separately within each time point, based on observed data only. If two or more subjects had the same rank (tie), the mean of the ranks of these observations was assigned to each of these observations.

The MMRM model included UIE at baseline as a fixed covariate, treatment group as a factor, and a treatment-by-time interaction, with a random site effect. The model was implemented in PROC MIXED in SAS using restricted likelihood estimation method with unstructured covariance matrix. Formal statistical testing between Anturool 84 mg/day group vs. placebo group and 56 mg/day group vs. placebo group were based on LS mean difference of the (rank transformed) mean change from

baseline in UIE per week at Week 12. The two secondary efficacy endpoints were analyzed in the same way as the primary endpoint.

**Missing data handling:**

Missing values for diary data were estimated using the mean of remaining non-missing values for the 3-day interval as long as there was only 1 of 3 values missing. In case of 2 or 3 days of diary missing, the diary evaluation for that clinical visit was set to missing.

Missing void volumes and missing urinary urgency were not imputed for any urinary episodes. Any analysis performed for the urinary urgency or urinary void was based on observed values only and excluded those urinary episodes that had missing values for the corresponding endpoint.

If a patient had less than 2 days of void volume and urinary urgency data prior to randomization (i.e., baseline data), those patient will be excluded from the analysis of these parameters.

**Reviewer's comments:**

*Due to the non-normality of the efficacy data, the applicant applied the MMRM model on rank-transformed data. No literatures or references were submitted to support the validity of this analysis method on rank-transformed data.*

**3.2.3.2 Reviewer's analysis method for primary/secondary efficacy endpoints**

The reviewer's efficacy analyses were based on ITT population. In the analysis of change from baseline in an endpoint, patients who had at least one post-baseline record of that endpoint will be included.

Due to the non-normality of the data for the change from baseline in the number of UIE at each visit, the reviewer's analyses were also based on the rank-transformed UIE data. But in the reviewer's analysis, the rank transformed change from baseline in the number of UIE at Week 12 was analyzed by an analysis of covariance (ANCOVA) model with ranked baseline number of UIE as a covariate and treatment group as a factor. The comparison between Anturool 84 mg/day vs. placebo and 56 mg/day vs. placebo was based on the estimated LS mean difference of the (rank transformed) mean change from baseline in UIE per week at Week 12. Last observation carried-forward (LOCF) method was used to impute the missing values of number of UIE at Week 12 before transformation was done.

The secondary endpoints were analyzed in the same way using the ANOCVA model described above with the corresponding ranked baseline of the endpoint as a covariate and treatment group as a factor in the model.

## 3.2.4 Results and Conclusions

### 3.2.4.1 Applicant's analyses results

#### Primary efficacy endpoint

Table 4 shows the applicant's analyses results of the number of UIE at Week 12. At Baseline, the mean and median weekly UIEs were slightly lower in the Anturol 84 mg/day group compared to the other treatment groups; median values were 37.3 episodes in the Anturol 84 mg/day group, (b) (4) and 42.0 episodes in the placebo group. At Week 12, median change from baseline in number of UIE per week were -18.7 (b) (4) episodes in the Anturol 84 mg/day (b) (4), compared with -16.3 episodes in the placebo group.

In the analysis of change from baseline in the number of UIE per week (using rank transformation on values), the p-value was 0.0333 (< 0.05, which was protocol specified level) for the comparison between Anturol 84 mg/day and placebo based on the estimated least square (LS) mean differences from MMRM model.

Table 4 - Analysis of change from baseline in UIE at Week 12 - Modified ITT Population

Weekly UIE	Anturol 84 mg/day	(b) (4)	Placebo
Baseline			
n	195		166
Mean(SD)	43.6 (27.50)		45.8 (28.85)
median	37.3		42.0
Change from baseline at Week 12			
n	163		133
mean	-21.9 (25.12)		-20.0 (27.02)
median	-18.7		-16.3
p-value <sup>1</sup> vs. placebo	<b>0.0333</b>		

Source: Table 10 (page 69) in the applicant's study report for 20070060.

1. P-value is based on the estimated LS mean difference at Week 12 from the MMRM model on rank-transformed data.

#### Reviewer's comment:

- (1) According to the applicant's pre-specified multiplicity controlling method (Page 32-34, statistical analysis plan (SAP) dated June 10th, 2010), the estimated least square (LS) mean differences on ranks (from MMRM model) between Anturol 84 mg/day and placebo is statistically significant (p-value = 0.0333, which was less than the protocol pre-specified 0.05 level, 2-sided). Hence the comparison between Anturol 84 mg/day and placebo on the secondary endpoints can proceed.

(b) (4)

- (3) The applicant submitted a memo (dated 24 August 2010) in the NDA submission to amend the testing strategy on the primary and secondary efficacy endpoints for the two Anturol doses. As this amendment occurred after the study data was unblinded (June 21, 2010). Therefore, this post-hoc memo was not acceptable for consideration in the statistical review by the reviewer.

### Secondary efficacy endpoints

At baseline, the mean and median average daily urinary frequencies were similar across all treatment groups (Table 5); median values were 10.7 micturitions in the Anturol 84 mg/day group, (b) (4) and 10.5 micturitions in the placebo group. At Week 12, median change from baseline in average daily urinary frequency were -2.7 (b) (4) micturitions experienced by patients in the Anturol 84 mg/day (b) (4) compared with -2.0 micturitions in the placebo group.

In the analysis of the change from baseline at Week 12 in average daily urinary frequency (using the rank transformation), the p-value was 0.0005 (< 0.0125, protocol pre-specified level) for the comparison between Anturol 84 mg/day and placebo.

Table 5 - Analysis of change from baseline in average daily urinary frequency at Week 12  
- Modified ITT Population

Average Daily Urinary Frequency	Anturol 84 mg/day	(b) (4)	Placebo
Baseline			
n	195		166
Mean(SD)	11.4 (2.86)		11.3 (2.87)
median	10.7		10.5
Change from baseline at Week 12			
n	163		133
mean	-2.9 (2.59)		-1.9 (2.88)
median	-2.7		-2.0
p-value <sup>1</sup> vs. placebo	<b>0.0005</b>		

Source: Table 11 (page 72) in the applicant's study report for 20070060.

1. P-value is based on the estimated LS mean difference at Week 12 from the MMRM model on rank-transformed data.

At baseline, the mean and median urinary volume per void was similar across all treatment groups (Table 6); median values were 189.0 mL in the Anturol 84 mg/day group, (b) (4) and 182.6 mL in the placebo group. At Week 12, median change from baseline in urinary volume per void were 24.3 (b) (4) in the Anturol 84 mg (b) (4) compared with 5.4 mL in the placebo group.

In the analysis of the change from baseline at Week 12 in urinary volume per void (using rank transformation), the P-value was 0.0017 (< 0.0125, protocol pre-specified level) for the comparison between Anturol 84 mg/day and placebo.

Table 6 - Analysis of change from baseline in average urinary void volume (mL) per void at Week 12  
- Modified ITT Population

Average Urinary Void Volume (mL) per void	Anturol 84 mg/day	(b) (4)	Placebo
Baseline			
n	190		162
Mean(SD)	196.5 (87.54)		182.0 (85.26)
median	189.0		182.6
Change from baseline at Week 12			
n	157		129
mean	29.0 (76.57)		10.4 (63.82)
median	24.3		5.4
p-value <sup>1</sup> vs. placebo	<b>0.0017</b>		

Source: Table 12 (page 74) in the applicant's study report for 20070060.

1. P-value is based on the estimated LS mean difference at Week 12 from the MMRM model on rank-transformed data.

**Reviewer's comments:**

(1) According to the applicant's pre-specified multiplicity controlling method, the estimated least square (LS) mean differences in the ranked change from baseline in average daily urinary frequency at Week 12 (from MMRM model) between Anturol 84 mg/day and placebo (p-value = 0.0005) was statistically significant at protocol pre-specified 0.0125 level, 2-sided.

(2) The estimated least square (LS) mean differences on the ranked change from baseline in average urinary void volume per void at Week 12 (from MMRM model) between Anturol 84 mg and placebo (p-value = 0.0017) was statistically significant at protocol pre-specified 0.0125 level, 2-sided.



(b) (4)

**3.2.4.2 Reviewer's analyses results**

The reviewer's analyses for each efficacy endpoint were conducted on the patients based on ITT population. The definition of ITT and MITT populations are shown in Table 7. The last three criteria for the applicant defined MITT population enriched the study population for efficacy analyses and may not represent the potential target population of drug use.

Table 7 - Definition of study populations

Population	Inclusion criteria
ITT (N=626)	<ul style="list-style-type: none"> <li>• Randomized in the study</li> <li>• Received at least one dose of any study drug</li> </ul>
MITT (N=532)	<ul style="list-style-type: none"> <li>• Properly randomized</li> <li>• Received at least one dose of study drug</li> <li>• Had completed urinary diary on 3 consecutive days at baseline and at least once at post-baseline period</li> <li>• Had an average of at least 1 urinary urge episode per day and an average of 8 or more voids per day at baseline</li> <li>• Had not used any prohibited prior and/or concomitant medication</li> </ul>

Source: Reviewer's summary based on the Applicant's definition on Page 17, Appendix 16.1.9 (Statistical analysis plan) in the applicant's study report for 20070060.

## Primary efficacy endpoint

At Week 12, median change from baseline in weekly UIEs were -16.4 episodes experienced by patients in the Anturol 84 mg group (b) (4), compared with -14.0 episodes in the placebo group; The LS mean difference between Anturol 84 mg and placebo in change from baseline in weekly UIEs (using rank transformation on values) was statistically significant (p-value=0.0445, at pre-specified 0.05 level, 2-sided), in favor of Anturol 84 mg/day, (b) (4)

Table 8 - Analysis of change from baseline in UIE at Week 12 - ITT Population (LOCF)

Weekly UIE	Anturol 84 mg/day	(b) (4)	Placebo
Baseline			
n	214		202
mean(SD)	43.6 (27.90)		45.8 (31.87)
Median	37.3		40.9
Change from baseline at Week 12			
n	211		192
mean(SD)	-20.4 (24.39)		-18.1 (28.81)
median	-16.4		-14.0
mean difference vs. placebo (SE)	-2.3 (2.65)		
p-value <sup>1</sup> vs. placebo	0.0445*		

Source: Statistical reviewer's analysis on ITT population.

<sup>1</sup> p-value is for the estimated LS mean difference vs. placebo from a rank-ANCOVA model with UIE baseline (rank) as a covariate, treatment as a factor.

\* p-value is significant at the 0.05 level, 2-sided.

## Secondary efficacy endpoints

At Week 12, median change from baseline in average daily urinary frequency were -2.3 micturitions in the Anturol 84 mg group (b) (4) compared with -1.7 micturitions in the placebo group; The LS mean difference between Anturol 84 mg and placebo in change from baseline in average daily urinary frequency (using rank transformation on values) is statistically significant (p-value=0.0010) at pre-specified 0.0125 level, 2-sided.

Table 9 - Analysis of change from baseline in average daily urinary frequency at Week 12 - ITT Population (LOCF)

Average daily urinary frequency	Anturol 84 mg/day	(b) (4)	Placebo
Baseline			
n	214		202
mean(SD)	11.3 (2.87)		11.5 (3.34)
median	10.7		11.0
Change from baseline at Week 12			
n	211		192
mean(SD)	-2.6 (2.66)		-1.9 (3.34)
median	-2.3		-1.7
mean difference vs. placebo (SE)	-0.7 (0.30)		
p-value <sup>1</sup> vs. placebo	0.0010*		

Source: Statistical reviewer's analysis on ITT population.

<sup>1</sup> p-value is for the estimated LS mean difference vs. placebo from a rank-ANCOVA model with urinary frequency baseline (rank) as a covariate, treatment as a factor.

\* p-value is significant at the 0.0125 level, 2-sided.

At Week 12, median change from baseline in average urinary void volume were 26.6 mL in the Anturol 84 mg group (b) (4) compared with 5.7 mL in the placebo group; The LS mean difference between Anturol 84 mg and placebo in change from baseline in average urinary void volume (using rank transformation on values) is statistically significant (p-value<0.0001) at pre-specified 0.0125 level, 2-sided.

Table 10 - Analysis of change from baseline in urinary void volume at Week 12 - ITT Population (LOCF)

<b>Average Urinary Void Volume (mL) per void</b>	<b>Anturol 84 mg/day</b>	(b) (4)	<b>Placebo</b>
Baseline			
n	209		197
mean(SD)	196.9 (88.11)		184.5 (85.71)
median	189.2		173.4
Change from baseline at Week 12			
n	206		187
mean(SD)	32.7 (77.25)		9.8 (64.98)
median	26.6		5.7
mean difference vs. placebo (SE)	23.0 (7.24)		
p-value <sup>1</sup> vs. placebo	<0.0001*		

Source: Statistical reviewer's analysis on ITT population.

<sup>1</sup> p-value is for the estimated LS mean difference vs. placebo from a rank-ANCOVA model with urinary void volume baseline (rank) as a covariate, treatment as a factor.

\* p-value is significant at the 0.0125 level, 2-sided.

### 3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

#### **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

There are no subgroup populations of interest in this submission.

#### **5. SUMMARY AND CONCLUSIONS**

Based on the protocol specified endpoints, i.e., the change from baseline in number of UIE, average daily urinary frequency and average urinary volume per void to Week 12, the results of study 20070060 provided statistical evidence of efficacy for the higher dose of Anturol 84 mg/day, but not for the lower dose of Anturol 56 mg/day after adjusting for type I error by pre-specified multiplicity controlling method. At Week 12, the median change from baseline were -16.4 episodes in weekly UIEs, -2.3 micturitions in average daily urinary frequency, and 26.6 mL in the average urinary void volume in the Anturol 84 mg group, compared with -14.0 episodes in weekly UIEs, -1.7 micturitions in average daily urinary frequency, and 5.7 mL in average urinary void volume in the placebo group.

## APPENDICES

### 1. Demographics

Table 11 - Patient demographics and baseline characteristics – ITT population

Characteristics	Treatment Group			Overall (N=626)
	Oxybutynin 84 mg/day (N=214)	Oxybutynin 56 mg/day (N=210)	Placebo (N=202)	
Age (years) <sup>1</sup>				
n	214	210	202	626
Mean (SD)	59.1 (13.34)	59.4 (12.63)	57.8 (13.31)	58.8 (13.10)
Median	60.0	59.0	59.0	59.0
Min, Max	24.0, 87.0	19.0, 89.0	21.0, 88.0	19.0, 89.0
Gender, n (%)				
Male	32 (15.0)	28 (13.3)	24 (11.9)	84 (13.4)
Female	182 (85.0)	182 (86.7)	178 (88.1)	542 (86.6)
Ethnicity, n (%)				
Hispanic or Latino	17 (7.9)	12 (5.7)	15 (7.4)	44 (7.0)
Non-Hispanic or Latino	197 (92.1)	198 (94.3)	187 (92.6)	582 (93.0)
Race, n (%) <sup>1</sup>				
American Indian or Alaska Native	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Asian	1 (0.5)	2 (1.0)	2 (1.0)	5 (0.8)
Black or African American	24 (11.2)	18 (8.6)	28 (13.9)	70 (11.2)
Native Hawaiian / Pacific Island	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.3)
White	183 (85.5)	187 (89.0)	172 (85.1)	542 (86.6)
Other	4 (1.9)	2 (1.0)	0 (0.0)	6 (1.0)
Height, cm				
n	214	210	202	626
Mean (SD)	164.6 (8.50)	164.9 (8.80)	163.7 (9.07)	164.4 (8.79)
Median	162.6	163.8	162.6	162.6
Min, Max	144.8, 193.0	142.2, 190.5	137.2, 191.8	137.2, 193.0
Weight, kg				
n	199	191	187	577
Mean (SD)	85.5 (21.11)	84.1 (20.20)	82.9 (21.97)	84.2 (21.09)
Median	81.6	80.7	78.0	80.7
Min, Max	41.7, 154.2	41.7, 138.3	40.3, 168.8	40.3, 168.8
Body Mass Index				
n	199	191	187	577
Mean (SD)	31.5 (7.29)	31.0 (6.99)	31.0 (7.91)	31.2 (7.39)
Median	30.1	30.0	29.6	29.9
Min, Max	17.4, 62.2	17.6, 51.6	18.6, 65.9	17.4, 65.9

Source: Section 14.1, Table 14.1.2

SD: standard deviation; Min: minimum; Max: maximum

<sup>1</sup> Age = Integer part of (Date of Birth – Date of informed consent) / 365.25.

Source: Table 7 (Page 64) in the applicant's study report for 20070060.

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/s/  
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JIA GUO  
11/29/2011

MAHBOOB SOBHAN  
11/30/2011

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 20-2513**

**Applicant: ANTARES PHARMA INC Stamp Date: Feb 8, 2011**

**Drug Name: Anturol  
(Oxybutynin Gel 3.0%)**

**NDA/BLA Type: New**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		√		86.6% patients are females 93.0% patients are non-hispanic or latino 86.6% patients are white
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.	√			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

File name: 5\_Statistics Filing Checklist for a New NDA\_202513

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**Potential review issues noted:**

1. The analysis results for the primary efficacy endpoint (rank transformed) on mITT population are statistically significant, in favor of oxybutynin, but the results for PP population are not statistically significant comparing oxybutynin with placebo.

**Requests to the Applicant on 74-day letter:**

1. Please submit tabulation data (i.e. raw data), statistical programs to derive the efficacy endpoints and population flags, and statistical programs to carry out efficacy analyses of primary and secondary endpoints.

**Brief summary of controlled clinical trials**

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint / Analysis	Sponsor's findings
20070060	Phase 3, randomized, placebo-controlled, double-blind, parallel, multicenter, open label extension	Randomized: Oxybutynin 84mg: 214 Oxybutynin 56mg: 210 Placebo: 202	Primary endpoint: the change from baseline to Week 12 in the number of urinary incontinence episodes (UIE) per week, as determined from a 3-day patient daily diary( The weekly average UIE is daily average UIE times 7)  Primary analysis: MMRM on rank transformed UIE with fixed effects for baseline UIE rank, treatment, study week, and study week by treatment interaction, random effect for pooled site.	<b>MITT population</b> Sample size: Oxybutynin 84mg: 195 Oxybutynin 56mg: 171 Placebo: 166 Median; Oxybutynin 84mg: -18.7 Oxybutynin 56mg: -21.0 Placebo: -16.3 P value vs. placebo (MMRM model on ranked UIE) Oxybutynin 84mg: 0.0333 Oxybutynin 56mg: 0.0283  <b>PP population</b> Sample size: Oxybutynin 84mg: 147 Oxybutynin 56mg: 132 Placebo: 105 Median; Oxybutynin 84mg: -18.7 Oxybutynin 56mg: -18.7 Placebo: -16.3 P value vs. placebo (MMRM model on ranked UIE) Oxybutynin 84mg: 0.2704 Oxybutynin 56mg: 0.3387

Jia Guo, Ph.D. 04/04/2011  


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 Reviewing Statistician Date

Mahboob Sobhan, Ph.D. 04/04/ 2011  


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 Supervisor/Team Leader Date

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/s/  
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JIA GUO  
04/04/2011

MAHBOOB SOBHAN  
04/04/2011