CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-204

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-204	Submission Date(s)	March 26, 2008; September 11, 2008; December 24, 2008
Brand Name		Gelnique®	
Generic Name		Oxybutynin chloride	
Reviewer		LaiMing Lee, Ph.D.	
Team Leader		Myong-Jin Kim, Pharm.D.	
OCP Division		Division of Clinical Pharmacology 3	
OND Division		Division of Reproductive and Urologic Products	
Sponsor		Watson Laboratories, Inc.	
Relevant IND and NDA		IND 50,489 and NDA 21-351	
Submission Type; Code		Original, S	
Formulation; Strengths; Regimen		Topical gel, 10%; each 1 gram gel sachet (1.14 mL) contains 100 mg oxybutynin chloride; apply one sachet once daily to dry intact skin on the abdomen, upper arms/shoulders, and thighs.	
Proposed Indication		Treatment of Overactive Bladder	

An Optional Inter-Division Level OCP Briefing was held on December 18, 2008 in Bldg 51, Rm 3300 and was attended by E. Dennis Bashaw, John Lazor, Myong-Jin Kim, George Benson, Christine Nguyen, Sandhya Apparaju, Hyunjin Kim, Ting Eng Ong, Doahn Tran, and Chongwoo Yu.

Table of Contents

1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 has reviewed NDA 22-204 for Oxybutynin Topical Gel (OTG) submitted to the Agency on March 26, 2008. We have found this NDA acceptable from a clinical pharmacology perspective. The pending issue is agreement from the sponsor on the Agency's proposed recommendations on the label.

1.2 Phase IV Commitments

There are no additional Clinical Pharmacology Phase IV commitments beyond those required under the Pediatric Research Equity Act (PREA).

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Oxybutynin chloride is an anticholinergic agent used for the treatment of Overactive Bladder (OAB). It is an antimuscarinic agent that has been previously approved as an immediate release (IR) oral tablet (Ditropan®), extended release (ER) oral tablet (Ditropan XL®), oral syrup (Ditropan®), and ER transdermal patch (Oxytrol®). The sponsor, Watson Laboratories, currently markets 39 cm^2 Oxytrol® transdermal patch and has designed OTG to have similar pharmacokinetic (PK) characteristics to those of Oxytrol®. The dosing recommendation for Oxytrol® is one patch applied twice weekly (once every 3 to 4 days). The sponsor states that an unoccluded gel system was considered to be potentially more convenient to use and should produce less skin irritation compared to the patch. The proposed daily dose is 1 gm of 10% OTG applied to the abdomen, upper arms/shoulders, or thigh with the recommendation to rotate the application sites.

The initial formulation and dose for OTG was 3 gm of 4.4% OTG. Through a steady-state PK analysis the initial formulation was found to provide an average plasma concentration of oxybutynin (OXY) comparable to Oxytrol®. The sponsor decided to explore the development of a higher concentration of OTG in an effort to reduce the application volume. The formulation and dose used in the clinical trials and the proposed to-be-market product is 1 gm of 10% OTG.

This Clinical Pharmacology review assessed the NDA for single and multiple dose PK, multiple dose relative bioavailability of OTG and Oxytrol®, multiple dose relative bioavailability of OXY and N-desethyloxybutynin (DEO) at three different application sites (abdomen, upper arms/shoulders, and thigh), and extrinsic factors such as person-to-person transference, use of sunscreen, and effect of showering. DEO is the major active metabolite of OXY with pharmacological activity on the human bladder detrusor muscle that is similar to that of OXY in *in vitro* studies.

Single Dose Pharmacokinetics: The sponsor conducted a single dose PK study to evaluate the PK parameters of 1 gm of 10% OTG.

The following table 1 summarizes mean (SD) PK parameters for OXY and DEO following a single dose application of OTG to the abdomen.

	AUC_{0-144} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
OXY	116.17 (39.47)	2.63 (1.02)	27.60 (10.21)	31.62 (19.43)
DEO	103.29 (48.64)	2.15 (1.04)	30.40 (13.94)	28.09 (9.35)

Multiple Dose Pharmacokinetics: Steady state was reached within 7 days. Following multiple doses of 1 gm of 10% OTG applied to rotating sites on the abdomen, upper arm/shoulder, and thigh, the mean (SD) AUC_{0-96} and C_{max} for OXY were 321.7 (112.3) ng.hr/mL and 5.99 (2.58) ng/mL, respectively.

The following table 2 summarizes mean (SD) PK parameters for OXY and DEO following multiple doses of OTG during the final four days of treatment.

	AUC_{0-96} (ng·hr/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)
OXY	321.7 (112.3)	3.35 (1.17)	5.99 (2.58)
DEO	246.4 (96.96)	2.57 (1.01)	4.35 (2.30)

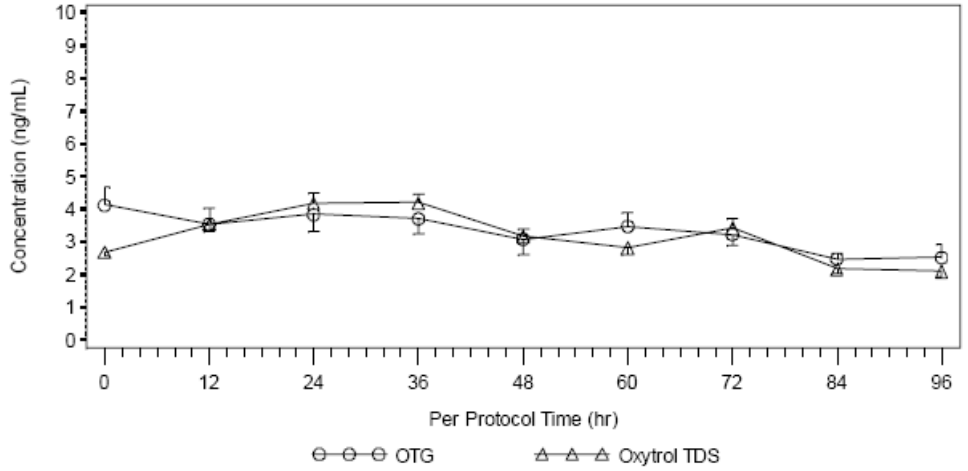
Relative Bioavailability of OTG and Oxytrol®: With the goal of achieving comparable systemic exposure of OXY and DEO with daily application of 1 gm 10% of OTG and twice weekly application of 39 cm^2 Oxytrol®, the sponsor compared the PK of OTG and Oxytrol® during multiple dose study. The mean (SD) AUC_{0-96} for OXY after applications of OTG and Oxytrol® were 321.7 (112.3) and 312.5 (67.62) ng.hr/mL, respectively. The mean (SD) AUC_{0-96} for DEO after applications of OTG and Oxytrol® were 246.4 (96.96) and 338.0 (116.9) ng.hr/mL, respectively. The mean (SD) C_{avg} for OXY for OTG was 3.35 (1.17) ng/mL, which is comparable to that observed with multiple doses of Oxytrol® (3.26 (0.70) ng/mL)) (Table 3); however, the number of blood samples taken to determine AUC_{0-96} and C_{avg} were sparse (Figure 1). Based on the product label for Oxytrol®, the mean (SD) C_{avg} for OXY following multiple dosing was 4.2 (1.1) ng/mL.

The following table 3 summarizes mean (SD) PK parameters for OXY following multiple doses of OTG and Oxytrol®.

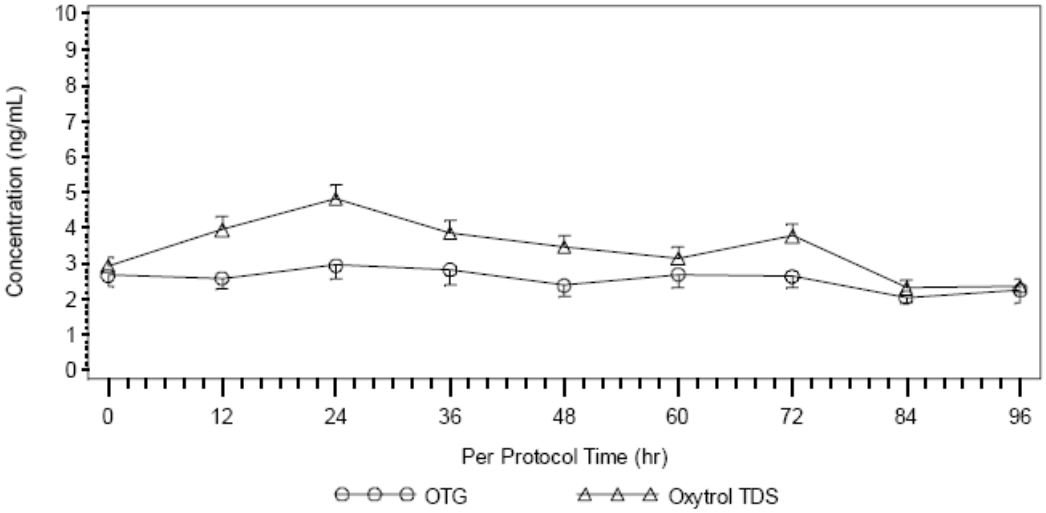
PK Parameter Mean (SD)	OTG 1 gm of 10%	Oxytrol® 39 cm^2
AUC_{0-96} (ng·hr/mL)	321.7 (112.03)	312.5 (67.62)
C_{avg} (ng/mL)	3.35 (1.17)	3.26 (0.70)
C_{max} (ng/mL)	5.99 (2.58)	4.82 (1.31)

The following figures present the plasma concentration vs. time profiles for OXY and DEO following 18 doses of 1 gm of 10% OTG (applied daily to rotating sites on the abdomen, upper arms/shoulders, and thigh) and 5 doses of Oxytrol® (applied every 3.5 days applied to rotating sites on the abdomen, hip, and buttocks) during the final four days of treatment (days 15-18).

The following figure 1 is the mean ± SEM plasma concentration vs. time profiles for OXY following multiple applications of OTG and Oxytrol®.



The following figure 2 is the mean ± SEM plasma concentration vs. time profiles for DEO following multiple applications of OTG and Oxytrol®.



Relative Bioavailability at Different Application Sites:
The following table 4 is a summary of mean (SD) steady-state PK parameters for OXY following application of 1 gm of 10% OTG to three different application sites (the abdomen, upper arms/shoulders, and thigh).

Application Site	AUC_{0-24} (ng.hr/mL)	C_{max} (ng/mL)	C_{avg} (ng/mL)
Abdomen	112.7 (58.00)	6.8 (3.93)	4.7 (2.39)
Upper Arm/Shoulder	133.8 (81.58)	8.3 (5.97)	5.5 (3.37)
Thigh	125.1 (84.67)	7.0 (4.95)	5.2 (3.50)

These results show that the PK parameters comparing application sites for OXY absorption at all three sites to be similar; however, only bioequivalence was demonstrated between the thigh and abdominal sites based on the 90% confidence intervals for OXY AUC_{0-24} and C_{max}. DEO concentrations were not

bioequivalent between thigh and abdominal sites, or for the upper arms/shoulders and abdomen for either PK parameters. Despite the small differences and taken into account the data variability, the bioavailability of OXY is similar at all three application sites and justifies the sponsor's recommendation to rotate sites. In addition, the efficacy and safety of OTG for the treatment for OAB was evaluated in a phase 3, multi-center, double-blind, placebo-controlled, 12-week clinical study by applying 1 gm of 10% OTG daily to rotating sites on the abdomen, upper arms/shoulders, or thigh.

In this study to assess bioavailability at different application sites the C_{avg} ranged from 4.7 to 5.5 ng/mL, which is relatively higher than the C_{avg} of 3.35 ng/mL observed from the multiple dose study.

Pediatric Plan: In the original NDA submission (March 26, 2008), the sponsor submitted a request for waiver of pediatric studies in children from birth through 4 years of age and a request for deferral of pediateric studies in children 5 to 17 years old until the OTG product is approved for use in adults. The Division of Reproductive and Urologic Products recommended a pediatric waiver in children birth to 4 years old and a pediatric deferral in children 5 to 17 years old; FDA's Pediatric Review Committee (PeRC) concurred with the Division's recommendation on January 14, 2009. The details on the specifics of the new protocols require additional discussions with the Sponsor.

Geriatric: In the phase 3 study, there were 243 patients under 65 years old (approximately 65%) and 137 patients over or equal to 65 years old (approximately 35%) who completed OTG treatment. According to the Medical Reviewer, there were no differences in safety or efficacy observed between those < 65 and $\underline{\geq}$ 65, and that dose adjustment in patients greater than or equal to 65 years is not necessary.

Gender and Race: In the phase 3 double-blind clinical trial, there were a total of 400 patients (352 females and 48 males) in the Safety Population of the placebo-controlled group. There were 335 Caucasians, 54 African-Americans, 7 Asians, 1 American Indian/Alaska Native, and 3 multiracials. In the phase 3 double-blind clinical trial, there were a total of 389 patients (352 females and 37 males) in the Safety Population of the OTG treatment group. There were 346 Caucasians, 33 African-Americans, 6 Asians, 2 American Indians/Alaska Natives, and 2 multiracials. According to the Medical Reviewer, the number of male or non-Caucasian patients in the phase 3 study were too limited to meaningfully assess safety or efficacy based on gender or race.

Person-to-Person Transfer: Drug transfer and absorption occurred in all 12 untreated subjects following vigorous and sustained skin-to-skin contact for 15 minutes; whereas clothing minimized and, in most cases (12 of 14), completely inhibited the absorption of OXY in untreated subjects. For untreated subjects not clothed, the mean (SD) AUC_{0-48} after skin-to-skin contact was 29.78 (24.46) ng.hr/mL, whereas the untreated subjects covered with clothing had a mean (SD) AUC_{0-48} was 0.24 (0.62) ng.hr/mL. The recommendation is that the application site should be covered with clothing once OTG has dried, in order to prevent transfer of OXY to an untreated person.

Use of Sunscreen: The sponsor demonstrated that applying the sunscreen either 30 minutes before or 30 minutes after single dose application of OTG did not affect the systemic exposure of OXY and DEO in 14 healthy subjects. The mean AUC_{0-72} for OTG alone, sunscreen before OTG, and sunscreen after OTG was 84.49, 91.18, and 83.55 ng.hr/mL, respectively. The mean C_{max} for all three treatment groups was similar and ranged from 2.66 to 3.02 ng/mL, while the T_{max} was also similar with a range from 23.43 to 23.71 hour. Based on these findings, the concomitant application of sunscreen, either before or after OTG application, had little effect on PK of OXY and DEO. Therefore, the recommendation is that OTG can be used without regard to the order of application with sunscreen.

The following tables 5 & 6 summarize the mean (SD) PK parameters for OXY and DEO before and after sunscreen application.

PK parameters for OXY Mean (SD)	OTG alone	Sunscreen before OTG	Sunscreen after OTG
AUC_{0-72} (ng.hr/mL)	84.49 (48.62)	91.18 (55.45)	83.55 (41.37)
C_{max} (ng/mL)	2.66 (1.73)	3.01 (2.02)	3.02 (1.85)
T_{max} (hr)	23.43 (4.93)	25.71 (4.07)	23.71 (5.54)

PK parameters for DEO Mean (SD)	OTG alone	Sunscreen before OTG	Sunscreen after OTG
AUC_{0-72} (ng.hr/mL)	73.13 (58.25)	80.88 (58.75)	69.55 (53.16)
C_{max} (ng/mL)	2.17 (1.75)	2.31 (1.74)	2.18 (1.71)
T_{max} (hr)	24.71 (5.74)	27.43 (1.45)	22.57 (8.99)

Showering: Based on the data presented on the effect of showering, the overall systemic exposure of OXY and DEO following OTG application was not significant. The largest difference in the mean (SD) AUC_{0-24} (15.6% lower) was observed for the showering 2-hours post-dose group compared to the no shower group (113.5 (62.48) vs. 134.7 (84.99) ng.hr/mL); however, there was significant variability observed with all the individual subjects in both groups. Showering after application does appear to alter the t_{max}, bringing it closer to the time of showering, presumably due to a transient increase in peripheral blood flow in response to the heat from the shower. Patients are advised to wait one hour after application of OTG before showering, bathing, swimming, or immersing the application site into water.

The following tables 7 & 8 summarize the effect of showering on the mean (SD) PK parameters for OXY and DEO following multiple doses of OTG.

	Shower Regimen			
PK parameters for OXY Mean (SD)	No shower	Shower 1 hour post-dose	Shower 2 hour post-dose	Shower 6 hour post-dose
AUC_{0-72} (ng.hr/mL)	134.4 (84.99)	132.8 (84.74)	113.5 (62.48)	147.2 (69.62)
C_{max} (ng/mL)	8.58 (5.74)	9.17 (6.43)	6.49 (3.30)	10.10 (6.49)
T_{max} (hr)	12.30 (11.70)	3.13 (2.10)	5.63 (4.02)	8.03 (7.79)

	Shower Regimen			
PK parameters for DEO Mean (SD)	No shower	Shower 1 hour post-dose	Shower 2 hour post-dose	Shower 6 hour post-dose
AUC_{0-72} (ng.hr/mL)	130.8 (111.7)	131.4 (103.2)	122.5 (98.32)	130.3 (85.62)
C_{max} (ng/mL)	7.04 (5.67)	7.18 (5.11)	6.41 (5.21)	7.12 (5.11)
T_{max} (hr)	15.27 (11.10)	3.70 (2.13)	8.40 (6.77)	7.40 (6.80)

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Symptoms of OAB include frequency and urgency, with or without urge or reflex incontinence, in the absence of local pathologic or metabolic factors that would account for these symptoms.

Oxybutynin chloride is an anticholinergic agent used for the treatment of OAB. It is an antimuscarinic agent that has been previously approved as an IR oral tablet (Ditropan®), ER oral tablet (Ditropan XL®), oral syrup (Ditropan®), and ER transdermal patch (Oxytrol®). The sponsor claims that 1 gram of 10% OTG administered daily was effective in the treatment of OAB as measured by significant reductions in the number of daily incontinence episodes, daily urinary frequency, and increase in volume per void. Additionally, the sponsor states the most frequently reported treatment-related adverse events in patients receiving OTG were dry mouth (6.9%) and application site reaction (2.1%). Moreover, the sponsor states that treatment with OTG was associated with a lower incidence of both anticholinergic and application site adverse events, compared to the transdermal patch.

Watson currently markets Oxytrol® transdermal patch and has designed the topical gel to have similar pharmacokinetic characteristics to those of Oxytrol®. The sponsor states that an unoccluded gel system was considered to be potentially more convenient to use and should produce less skin irritation compared to the patch. Optimization of the active drug substance concentration was achieved with in vitro skin permeation studies using gels with oxybutynin chloride concentrations of 22 mg/g (2.2%), 44 mg/g (4.4%), 66 mg/g (6.6%), 88 mg/g (8.8%) and 132 mg/g (13.2%). The greatest increase in flux occurred between 2.2% and 4.4% while concentrations greater than 4.4% showed no significant effect on OXY skin flux.

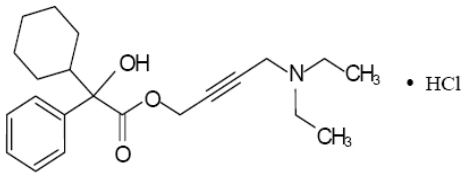
Watson also conducted a pilot in vitro bioavailability study using human cadaver skin and concluded that an average of 2.9% of the applied dose is absorbed across the skin over 24 hours. Based on this finding, it was estimated that 3.36 gm (4.2 mL) of a 4.4% gel would be required to deliver an equivalent amount of OXY to achieve equivalent systemic concentrations of OXY as the Oxytrol® transdermal patch. To reduce the application volume, Watson later reformulated the product that resulted in a (b) (4) 1 gm sachet of 10% OXY.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The active ingredient of OTG is oxybutynin chloride, which is a white to off white crystal that is freely soluble in water and alcohol. Oxybutynin chloride is a racemic molecule consisting of the R and S enantiomeric forms; both forms are used in drug product.

The molecular weight is 357. The empirical formula is $C_{22}H_{31}NO_3 \cdot HCl$

The following is the structural formula:



The formulation of the to-be-marketed OTG, 10% is listed in the following table 8.

Component	% by Weight	mg/g	Function
Oxybutynin chloride, USP	10.0	100	Drug Substance
Purified Water, USP		(b) (4)	
Alcohol, USP			
Glycerin, USP			
Sodium Hydroxide, (b) (4) (Sodium Hydroxide, NF and Purified Water, USP)			
Hydroxypropyl Cellulose, NF			

As described above, other formulations were studied in the early stages of product development to evaluate initial proof-of-concept, dosing efficiency, and pharmacokinetics.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

OXY acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. The effect on the bladder detrusor muscles is a relaxation of involuntary contractions resulting in increased maximum urinary bladder capacity and increased the volume to first detrusor contraction. Therefore, OXY is expected to decrease urinary urgency and the frequency of both incontinence episodes and voluntary urination. The sponsor is seeking approval of 1 gm of 10% OTG for the treatment of OAB. The product will be available in 1 gram (1.14 mL) sachets containing 100 mg oxybutynin chloride.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To achieve comparable systemic exposure of OXY and DEO with daily application of 1 gm 10% of OTG and twice weekly application of 39 cm^2 Oxytrol®, the sponsor conducted a multiple dose relative bioavailability study. Based on the findings from this study, a phase 3 study evaluating the efficacy and safety of 1 gm 10% OTG was conducted.

2.2.2 What are the clinical endpoints measured in the phase 3 clinical study?

The primary efficacy clinical endpoint of daily treatment of a 1 gm dose of 10% OTG during a 12-week clinical study for the treatment of OAB is the change from baseline to endpoint (Week 12 Last Observation Carried Forward) in the number of urinary incontinence episodes per day recorded on a 3-day urinary dairy versus placebo group. The secondary endpoints are the changes in average urinary frequency, average urinary volume per void from baseline to endpoint, and average nocturia episodes

along with two Quality of Life instruments (the Incontinence Impact Questionnaire (IIQ) and the King's Health Questionnaire (KHQ)).

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. OXY is the main active moiety of OTG. DEO is the major metabolite of OXY with pharmacological activity similar to OXY *in vitro*. The sponsor reported the plasma OXY and DEO concentrations in the PK studies.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure (dose)-response relationships for efficacy?

The sponsor designed the majority of the formulations to provide comparable systemic exposure of OXY and DEO as delivered by Oxytrol®. As such, there were no formal dose ranging, dose-response, or concentration-response evaluations conducted for efficacy.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

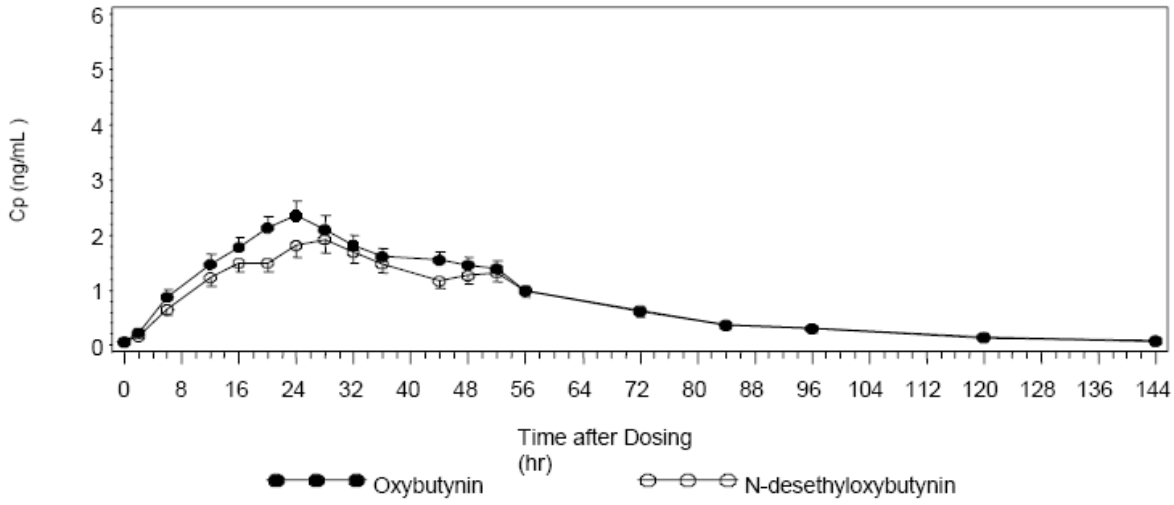
The sponsor designed the majority of the formulations to provide comparable systemic exposure of OXY and DEO as delivered by Oxytrol®. As such, there were no formal dose ranging, dose-response, or concentration-response evaluations conducted for safety.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the single dose PK parameters?

The initial formulation and dose for OTG was 3 gm of 4.4% OTG. Through a steady-state PK analysis, this initial formulation was found to provide an average plasma concentration of OXY and DEO comparable to Oxytrol®. Based on the PK study, the elimination half-life values for OXY and DEO are approximately 24 and 33 hours, respectively (Study OG03005). In order to minimize the application volume while maintaining the same amount of drug absorbed, Watson developed a more concentrated gel formulation (10%) and estimated that approximately 1.5 gm of 10% gel would match the plasma concentration of OXY obtained from the previously evaluated 3 gm of 4.4% gel formulation. In study OG04007, Watson evaluated single dose PK of OXY and DEO following application of 1 gm of 10% OTG on the abdomen.

The following figure 3 is the mean ± SEM plasma concentration vs. time profiles for OXY and DEO following a single dose application of OTG to the abdomen.



The following table 9 summarizes the single dose PK parameters for OXY and DEO following application of OTG to the abdomen.

PK Parameter Mean (SD)	AUC_{0-144} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
OXY	116.17 (39.47)	2.63 (1.02)	27.60 (10.21)	31.62 (19.43)
DEO	103.29 (48.64)	2.15 (1.04)	30.40 (13.94)	28.09 (9.35)

2.2.5.2 What are the multiple dose PK parameters?

Multiple Dose PK

In a multiple dose PK study the sponsor evaluated the steady-state plasma concentrations of OXY and DEO following application of 1 gm of 10% OTG (Study OG06005). Twenty subjects (12 males and 8 females) completed both treatment periods. The mean (SD) age was 25.4 (8.07) years with a range from 18 to 44 years. The study consisted of 18 days of treatment with either OTG (applied daily) applied to rotating sites on the abdomen, thighs, and upper arms. Blood samples were taken for plasma concentrations of OXY and DEO while the patients were still receiving daily treatment of OTG beginning on Day 15 and continued until Day 18 (for a total of 4 days).

The following table 10 presents the multiple dose PK parameters for OXY and DEO following application of OTG during the final four days of treatment.

PK Parameter Mean (SD)	AUC_{0-96} (ng·hr/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)
OXY	321.7 (112.3)	3.35 (1.17)	5.99 (2.58)
DEO	246.4 (96.96)	2.57 (1.01)	4.35 (2.30)

Relative Bioavailability of OTG and Oxytrol®

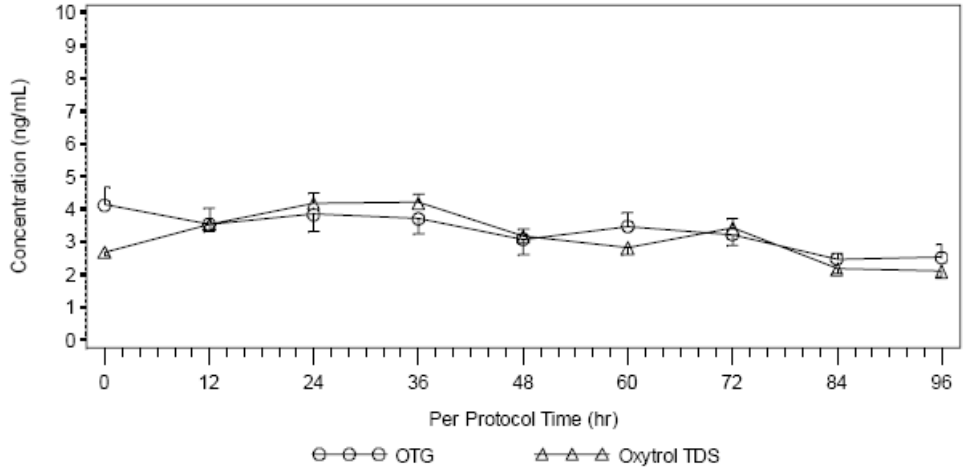
In the same study, the sponsor also evaluated the steady-state plasma concentrations of OXY and DEO following application of Oxytrol®. Subjects received five applications of Oxytrol® – one patch every 3.5 days applied to rotating sites on the abdomen, thighs, and upper arms. Blood samples were taken for plasma concentrations of OXY and DEO while the patients were treated with the final Oxytrol® patch beginning on Day 15 and continued until Day 18 (for a total of 4 days). During the final 96-hours dosing period, the mean AUC_{0-96} for OXY was 321.7 and 312.5 ng.hr/mL for OTG and Oxytrol®, respectively, which represents an insignificant (2.94%) higher exposure from OTG. The mean C_{avg} for oxybutynin delivered from OTG and Oxytrol TDS was similar at 3.35 and 3.26 ng/mL, respectively. The mean (SD) AUC_{0-96} and C_{max} for OXY were 321.7 (112.3) ng.hr/mL and 5.99 (2.58) ng/mL, respectively.

Based on the product label for Oxytrol®, the mean (SD) C_{avg} for OXY following multiple dosing was 4.2 (1.1) ng/mL. The mean (SD) C_{avg} for OXY for OTG was 3.35 (1.17) ng/mL, which is comparable to that observed with multiple doses of Oxytrol® from the same study; however, the number of blood samples taken to determine AUC_{0-96} and C_{avg} were sparse. There were only 9 blood samples taken over the 96 hour period (1 sample every 12-hour interval). In the study to assess bioavailability at different application sites (Study OG04008) where the PK parameters where calculated based on 8 blood samples taken over a 24 hour time frame, the AUC_{0-24} (average of the three sites) was 123.9 ng.hr/mL and C_{avg} ranged from 4.7 to 5.5 ng/mL.

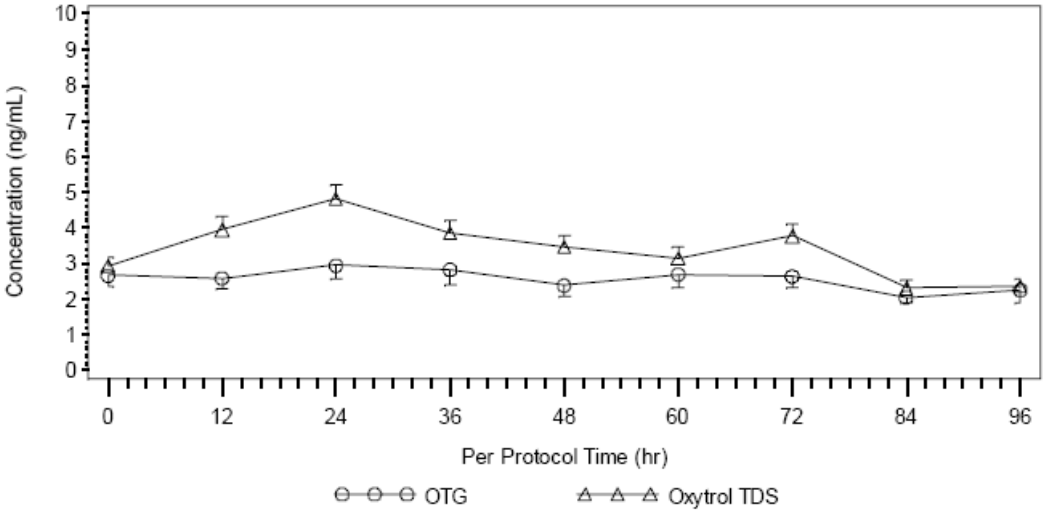
Extrapolating AUC_{0-24} over a 96 hour period with more frequent blood draws, the AUC_{0-96} is expected to be approximately 495.6 ng.hr/mL (AUC_{0-24} x 4 = 123.9 x 4 (study OG04008)) (not 321.7 ng.hr/mL) so it appears that the infrequent sampling over the 96 hour period in the multiple dose study OG06005 may have resulted in an under-estimation of the AUC_{0-96} and C_{avg}. Additionally, in Study OG06005, one of nine blood samples was not obtained from Subjects 1306 and 1309 following OTG application and one of nine blood samples was not obtained from Subjects 1307 and 1317 after Oxytrol® application which may have also contributed to the under-estimation of AUC_{0-96} and C_{avg}. It is the opinion of this reviewer that PK parameters determined from Study OG06005 do not accurately reflect the steady state plasma concentration vs. time profile for OXY and DEO following multiple applications of OTG and Oxytol® due to infrequent sampling and should not be included in the product label.

The following figures present the plasma concentration vs. time profiles for OXY and DEO following 18 doses of 1 gm of 10% OTG (applied daily to rotating sites on the abdomen, upper arms/shoulders, and thigh) and 5 doses of Oxytrol® (applied every 3.5 days applied to rotating sites on the abdomen, hip, and buttocks).

The following figure 4 is the mean ± SEM plasma concentration vs. time profiles for OXY following multiple applications of OTG and Oxytrol®



The following figure 5 is the mean ± SEM plasma concentration vs. time profiles for DEO following multiple applications of OTG and Oxytrol®



The following table 11 summarizes mean (SD) PK parameters for OXY following multiple doses of OTG and Oxytrol®.

PK Parameter Mean (SD)	OTG 1 gm of 10%	Oxytrol® 39 cm^2
AUC_{0-96} (ng·hr/mL)	321.7 (112.03)	312.5 (67.62)
C_{avg} (ng/mL)	3.35 (1.17)	3.26 (0.70)
C_{max} (ng/mL)	5.99 (2.58)	4.82 (1.31)

The following table 12 summarizes mean (SD) PK parameters for DEO following multiple doses of OTG and Oxytrol®.

PK Parameter Mean (SD)	OTG 1 gm of 10%	Oxytrol® 39 cm^2
AUC_{0-96} (ng·hr/mL)	246.4 (96.96)	338.0 (116.9)
C_{avg} (ng/mL)	2.57 (1.01)	3.52 (1.22)
C_{max} (ng/mL)	4.35 (2.30)	4.98 (1.68)

Multiple Dose Relative Bioavailability at Different Application Sites
In Study OG04008, the sponsor conducted a multiple dose, open-label, randomized study comparing the relative bioavailability of OXY following gel application to the abdomen, upper arm/shoulder and thigh with daily application of 1 gm 10% of OTG. Over the total 42 days of treatment, each subject was dosed with 1 gm of 10% OTG for 14 days per application site with no washout period before rotating to the next application site. For each treatment period, subjects received 13 days of outpatient gel applications followed by one day of inpatient gel application (on Days 14, 28, and 42). On the 14^{th} day of each treatment period, subjects returned to the clinic for 24 hours of inpatient serial blood sampling. After the final gel application in the third treatment period, subjects had 6 additional outpatient visits for single daily blood samples, which provided the PK profile for all three treatment arms from Days 42-49. Blood samples were taken for plasma concentrations of R- and S- OXY and R- and S- DEO and were taken within 30 minutes prior to the first inpatient dose, and at approximately 2, 4, 6, 8, 12, 16, 20, and 24 hours after the dose.

The mean plasma concentration for OXY and DEO fluctuated minimally following during the 24 hour dosing interval following 14 days of OTG daily application and were similar at the abdomen, thigh and upper arm/shoulder. The profiles for OXY and DEO were fairly flat for all three application sites with the mean C_{avg} for OXY ranging from 4.7 to 5.5 ng/mL, which is also similar to the mean (SD) C_{avg} for OXY of 4.2 (1.1) ng/mL following multiple dosing Oxytrol® (based on the product label).

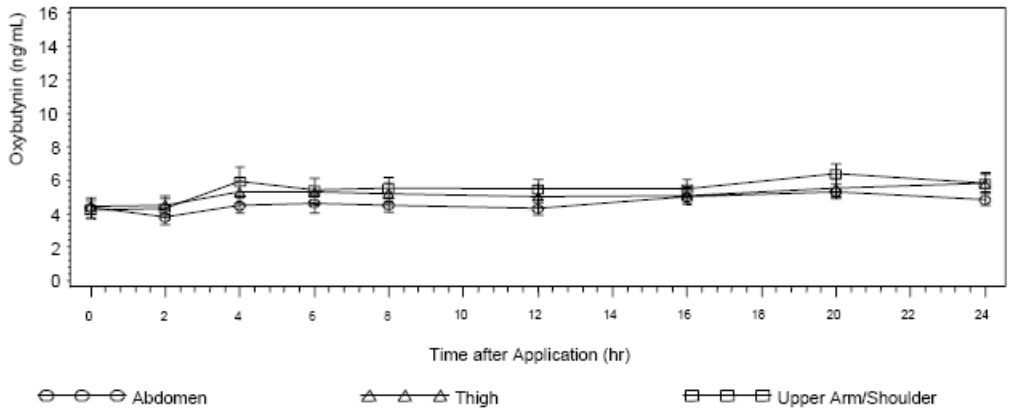
These results show that the PK parameters comparing application sites for OXY absorption at all three sites to be similar; however, only bioequivalence was demonstrated between the thigh and abdominal sites based on the 90% confidence intervals for OXY AUC_{0-24} and C_{max}. DEO concentrations were not bioequivalent between thigh and abdominal sites, or for the upper arms/shoulders and abdomen for either PK parameters. Despite the small differences and taken into account the data variability, the bioavailability of OXY and DEO is similar at all three application sites and justifies the sponsor's recommendation to rotate sites.

Additionally, during the 12-week phase 3, multicenter, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of daily dosing of OTG for the treatment of symptoms for OAB, 1 gm of 10% OTG was applied daily to rotating sites on the abdomen, upper arms/shoulders, or thigh.

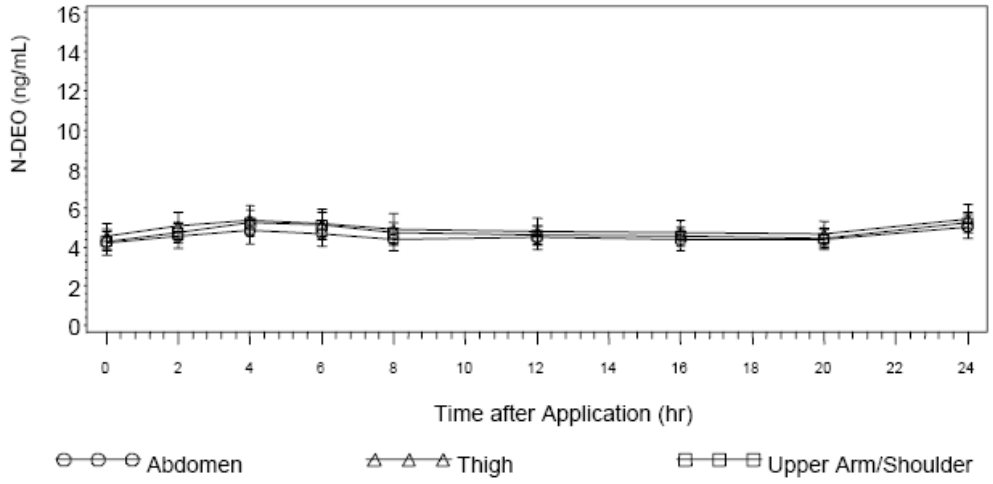
The following table 13 is a summary of mean (SD) steady-state PK parameters for OXY following application of OTG to three different application sites (abdomen, upper arms/shoulders, and thigh).

Application Site	AUC_{0-24} (ng.hr/mL)	C_{max} (ng/mL)	C_{avg} (ng/mL)
Abdomen	112.7 (58.00)	6.8 (3.93)	4.7 (2.39)
Upper Arm/Shoulder	133.8 (81.58)	8.3 (5.97)	5.5 (3.37)
Thigh	125.1 (84.67)	7.0 (4.95)	5.2 (3.50)

The following figure 6 is the mean ± SEM plasma concentration vs. time profiles for OXY for the abdomen, thigh, and upper arm/shoulder application sites.



The following figure 7 is the mean ± SEM plasma concentration vs. time profiles for DEO for the abdomen, thigh, and upper arm/shoulder application sites.



2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Renal insufficiency and hepatic insufficiency

The sponsor did not evaluate the impact of renal or hepatic impairment on the PK of OTG.

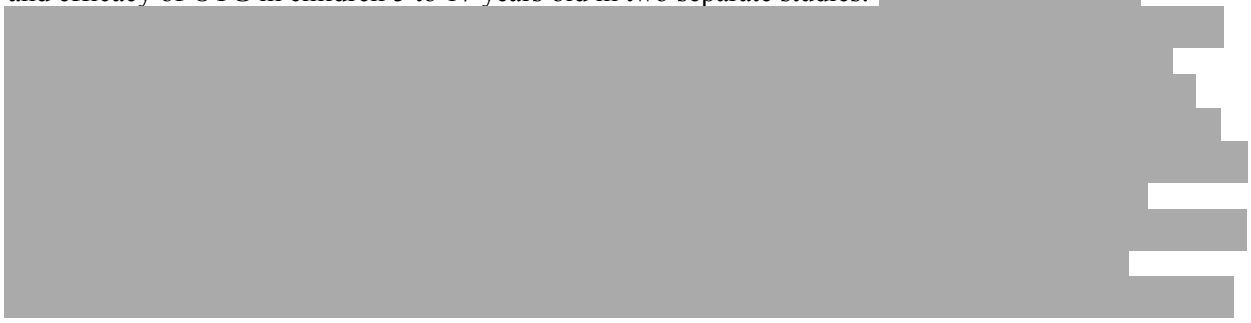
Geriatric

In the phase 3 study, there were 243 patients under 65 years old (approximately 65%) and 137 patients over or equal to 65 years old (approximately 35%) who completed OTG treatment. There were no differences in safety or efficacy observed in patients < 65 and ≥ 65 years of age, and that dose adjustment in patients greater than or equal to 65 years is not necessary (see Medical Review). The sponsor evaluated the relationship between plasma OXY concentrations and the primary clinical endpoint (change from baseline in efficacy parameters for urinary incontinence episodes) and age using linear regression. For patients with age less than 65 years, there was no correlation with OXY concentrations and urinary incontinence. For patients with age greater than or equal to 65 years, there was no correlation with OXY concentrations and urinary incontinence.

Pediatric

In the original NDA submission (March 26, 2008), the sponsor submitted a request for waiver of pediatric studies in children from birth through 4 years of age and a request for deferral of pediateric studies in children 5 to 17 years old until the OTG product is approved for use in adults. In a amendment to the NDA (September 11, 2008), the sponsor submitted a pediatric plan to evaluate OTG in children 5 to 17 years of age. The proposed PK study would be used to bridge the findings of Study O03010, which evaluated the efficacy and safety of Oxytrol® (at doses of 1.3 mg/day, 2.6 mg/day, and 3.9 mg/day) and oral oxybutynin at doses up to 15 mg/day, in children 6 to 15 years of age. The sponsor proposed an open-label, uncontrolled safety and PK study in approximately 40 children 5 to 17 years old with detrusor overactivity associated with a neurological condition (e.g. spina bifida). The study would evaluate two doses of OTG and allow dose titration. Either 0.5 g or 1 g 10% OTG would be applied once daily for 8 weeks. The Medical Reviewer stated that Study O03010, submitted to the Oxytrol® IND #50489, failed to demonstrate efficacy of Oxytrol® in pediatrics due to low sample size, target population, and inappropriate selection of efficacy primary endpoint. Therefore, the proposed PK study to bridge the safety findings in Study O03010 is unacceptable and the Division requested the Sponsor to submit a new plan.

In response to the Agency's request for a new pediatric plan, the Sponsor submitted a revised phase 4 pediatric protocol (dated December 24, 2008) to evaluate the pharmacodynamic (PD) and PK, and safety and efficacy of OTG in children 5 to 17 years old in two separate studies. (b) (4)



[redacted] (b) (4)

The Division of Reproductive and Urologic Products recommended a pediatric waiver in children birth to 4 years old and a pediatric deferral in children 5 to 17 years old; FDA's Pediatric Review Committee (PeRC) concurred with the Division's recommendation on January 14, 2009. The details on the specifics of the new protocols require additional discussions with the Sponsor.

Gender & Race

In the phase 3 double-blind clinical trial, there were a total of 400 patients (352 females and 48 males) in the Safety Population of the placebo-controlled group. There were 335 Caucasians, 54 African-Americans, 7 Asians, 1 American Indian/Alaska Native, and 3 multiracials. In the phase 3 double-blind clinical trial, there were a total of 389 patients (352 females and 37 males) in the Safety Population of the OTG treatment group. There were 346 Caucasians, 33 African-Americans, 6 Asians, 2 American Indians/Alaska Natives, and 2 multiracials. The number of male or non-Caucasian patients in the phase 3 study was too limited to meaningfully assess safety or efficacy based on gender or race (see Medical Review).

Body Mass Index

In the phase 3 study, the sponsor evaluated the relationship between plasma OXY concentrations and the primary clinical endpoint (change from baseline in efficacy parameters for urinary incontinence episodes) and body mass index (BMI) using linear regression. For patients with BMI less than 32 kg/m^2, there was no correlation with OXY concentrations and urinary incontinence.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (person-to-person transfer, use of sunscreen, and effect of showering) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

Person-to-Person Transfer

The potential for transfer of OXY and DEO after OTG application from a treated patient to an untreated person was evaluated in a single dose, open-label, randomized, parallel group design (Study OG06007). Fifty-two healthy male and female subjects were randomized to receive 1 gm of 10% OTG or no OTG. Those who received OTG treatment (14 males and 13 females) were further randomized to cover the application site or to remain unclothed following the application. Two scenarios were evaluated: one in which the treated and untreated subjects engaged in 15 minutes of sustained and direct skin-to-skin contact between the abdomen of the treated subject and the abdomen of the untreated subject; and another in which the treated subject wore clothing covering the application site during 15 minutes of sustained contact with the abdomen of the untreated subject (11 males and 14 females). Subjects were engaged in the direct physical contact 1 hour post-dose.

Drug transfer and absorption occurred in all 12 untreated subjects following vigorous and sustained skin-to-skin contact; whereas clothing minimized and, in most cases (12 of 14), completely inhibited the absorption of OXY in untreated subjects. For all subjects not clothed, the mean (SD) AUC_{0-48} for OXY after skin-to-skin contact was 29.78 (24.46) ng.hr/mL, whereas for all subjects covered with clothing had the mean (SD) AUC_{0-48} was 0.24 (0.62) ng.hr/mL. For DEO, the mean (SD) AUC_{0-48} was 0.00 (0.00) and

33.26 (36.04) ng.hr/mL for all subjects covered with clothing and for all subjects with skin-to-skin, respectively. The mean (SD) C_{max} was 0.00 (0.00) and 1.01 (1.05) ng/mL for all subjects covered with clothing and for all subjects with skin-to-skin contact, respectively.

Transfer of OXY and DEO occurred in both male and female subjects when there was direct skin-to-skin contact; however, female subjects generally absorbed more drug and attained higher mean maximum plasma oxybutynin concentrations than males when there was direct skin-to-skin contact. Because the untreated subjects did not receive direct application of OTG, these results do not truly reflect potential difference in absorption of OXY and DEO based on gender.

The recommendation is that the application site should be covered with clothing once OTG has dried in order to prevent transfer of OXY and DEO to an untreated person.

Table 14. Summary of PK for OXY following skin-to-skin contact.

PK Parameters Mean (SD)	All Subjects (n=12)	Female Subjects (n=7)	Male Subjects (n=5)
AUC_{0-48} (ng.hr/mL)	29.78 (24.46)	37.67 (29.00)	18.73 (11.06)
C_{max} (ng/mL)	0.94 (0.75)	1.14 (0.88)	0.66 (0.45)
T_{max} (hr)	17.27 (7.46)	15.70 (8.14)	19.47 (6.57)

Table 15. Summary of PK for OXY following clothing-to-skin contact.

PK parameters Mean (SD)	All subjects (n=14)	Female subjects (n=8)	Male subjects (n=6)
AUC_{0-48} (ng.hr/mL)	0.24 (0.62)	0.43 (0.80)	0.00 (0.00)
C_{max} (ng/mL)	0.01 (0.03)	0.02 (0.04)	0.00 (0.00)
T_{max} (hr)	8.27 (0.00)	8.27 (0.00)	---

Table 16. Summary of PK for DEO following skin-to-skin contact.

PK Parameters Mean (SD)	All Subjects (n=12)	Female Subjects (n=7)	Male Subjects (n=5)
AUC_{0-48} (ng.hr/mL)	33.26 (36.04)	47.10 (42.18)	13.89 (9.94)
C_{max} (ng/mL)	1.01 (1.05)	1.41 (1.23)	0.45 (0.31)
T_{max} (hr)	19.27 (6.18)	20.84 (5.86	17.07 (6.57)

Table 17. Summary of PK for DEO following clothing-to-skin contact.

PK parameters Mean (SD)	All subjects (n=14)	Female subjects (n=8)	Male subjects (n=6)
AUC_{0-48} (ng.hr/mL)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
C_{max} (ng/mL)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
T_{max} (hr)	---	---	---

Use of Sunscreen

The effect of sunscreen on the PK of OXY and DEO was studied in healthy male and female subjects using a three-period, open-label, randomized crossover design of single applications of 1 g of 10% OTG (Study OG06001). Fourteen subjects completed all three treatment periods (OTG alone, OTG application preceded by sunscreen application, and OTG application followed by sunscreen application). Each subject received 3 applications of 1 gm of 10% OTG applied by the subject to the abdomen with a predefined application area of 400 cm^2. Subjects also received co-administration of 800 mg of Coppertone® Oil-Free Sunblock Lotion Sun Screen Protection (SPF) 15 sunscreen lotion with OTG on 2 of the dosing days. Sunscreen application was completed 30 minutes before or 30 minutes after OTG application, based on the treatment sequence.

The sponsor demonstrated that applying the sunscreen either 30 minutes before or 30 minutes after single dose application of OTG did not affect the systemic exposure of OXY and DEO in 14 healthy subjects. The mean AUC_{0-72} for OTG alone, sunscreen before OTG, and sunscreen after OTG was 84.49, 91.18, and 83.55 ng.hr/mL, respectively. For OXY, the mean C_{max} for all three treatment groups was similar and ranged from 2.66 to 3.02 ng/mL, while the T_{max} was also similar with a range from 23.43 to 25.71 hour. Based on these findings, the concomitant use of sunscreen, either before or after OTG application, had little effect on PK of OXY and DEO. Therefore, the recommendation is that OTG can be used without regard to the order of application with sunscreen.

The following tables 18 & 19 summarize the mean (SD) PK parameters for OXY and DEO before and after sunscreen application.

PK parameters for OXY Mean (SD)	OTG alone	Sunscreen before OTG	Sunscreen after OTG
AUC_{0-72} (ng.hr/mL)	84.49 (48.615)	91.18 (55.451)	83.55 (41.368)
C_{max} (ng/mL)	2.66 (1.728)	3.01 (2.017)	3.02 (1.846)
T_{max} (hr)	23.43 (4.926)	25.71 (4.065)	23.71 (5.539)

PK parameters for DEO Mean (SD)	OTG alone	Sunscreen before OTG	Sunscreen after OTG
AUC_{0-72} (ng.hr/mL)	73.13 (58.254)	80.88 (58.750)	69.55 (53.163)
C_{max} (ng/mL)	2.17 (1.751)	2.31 (1.735)	2.18 (1.710)
T_{max} (hr)	24.71 (5.744)	27.43 (1.453)	22.57 (8.993)

Effect of Showering

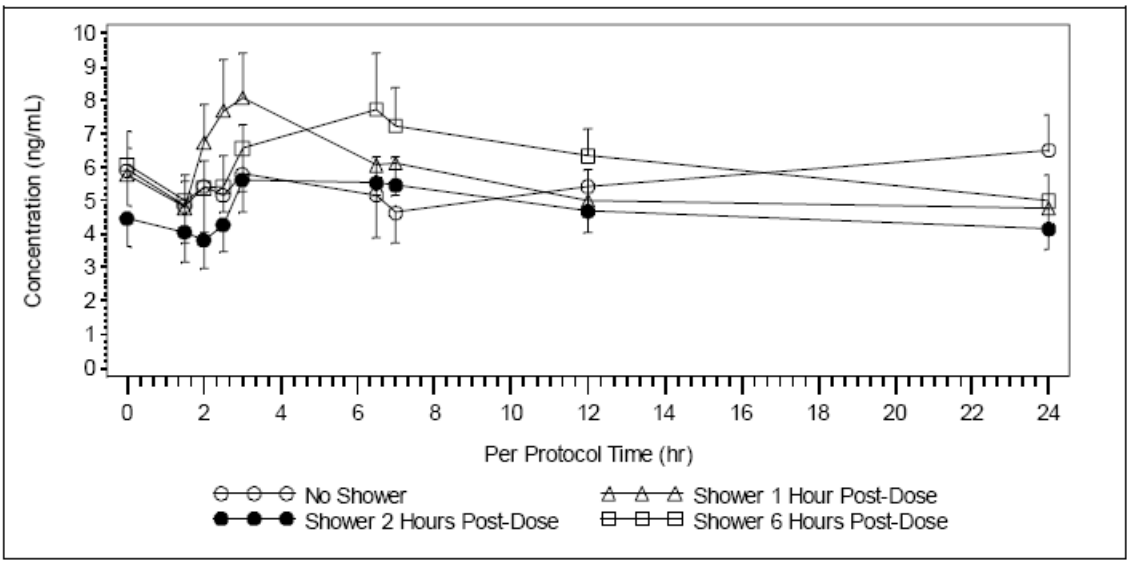
The effect of showering at various times after application of 1 g of 10% OTG on the bioavailability, PK, and metabolism of OXY was studied in a multiple-dose, open-label, randomized 4-way crossover design (Study OG06006). Fifteen subjects completed the study were instructed to apply OTG on the designated site and wash hands thoroughly after application. The study design consisted of daily outpatient dosing with 1 gm of 10% OTG for 35 consecutive days and included inpatient serial blood sampling for 24 hours on Days 14, 21, 28, and 35. Each subject received 35 daily applications of OTG applied to rotating sites on the abdomen, upper arm/shoulder, and thighs. Each showering session was 5 minutes in duration with the water temperature at 110°F and hypoallergenic soap.

Based on the data presented on the effect of showering, the overall systemic exposure of OXY and DEO following OTG application was not significant. The largest difference in the mean (SD) AUC_{0-24} (15.6% lower) was observed for the showering 2-hours post-dose group compared to the no shower group (113.5 (62.48) vs. 134.7 (84.99) ng.hr/mL; however, there was significant variability observed with all the individual subjects in both groups. Showering after application does appear to alter the T_{max}, bringing it closer to the time of showering, presumably due to a transient increase in peripheral blood flow in response to the heat from the shower. Patients are advised to wait one hour after application of OTG before showering, bathing, swimming, or emersing the application site into water.

The following table 20 summarizes the mean (SD) PK parameters for OXY for each showering regimen following multiple doses of OTG application.

	Shower Regimen			
PK parameters for OXY Mean (SD)	No shower	Shower 1 hour post-dose	Shower 2 hour post-dose	Shower 6 hour post-dose
AUC_{0-24} (ng.hr/mL)	134.4 (84.99)	132.8 (84.74)	113.5 (62.48)	147.2 (69.62)
C_{max} (ng/mL)	8.58 (5.74)	9.17 (6.43)	6.49 (3.30)	10.10 (649)
T_{max} (hr)	12.30 (11.70)	3.13 (2.10)	5.63 (4.02)	8.03 (7.79)
DEO:OXY	0.93 (0.38)	0.98 (0.32)	1.00 (0.39)	0.92 (0.41)

The following figure 8 is the mean ± SEM plasma OXY concentration vs. time profile for each showering regimen.



2.4.2 Drug-Drug Interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

It is known that oxybutynin is metabolized primarily by the CYP450 system, which is predominately found in the liver and GI tract. Like Oxytrol, OTG is administered topically and thus bypasses first-pass and hepatic metabolism, therefore potential interactions with drugs that inhibit or induce CYP3A4 is low. The sponsor did not investigate potential interactions with other topically applied drugs.

2.5 General Biopharmaceutics

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

(b) (4) The sponsor conducted a comparative bioavailability study (Study OG04007) using 3.9 mg/day (39 cm^2) Oxytrol®, 3 g of 4.4% OTG, 1 g of 10% OTG, and 3 g of 10% OTG. Each of these formulations produced measurable and therapeutic concentrations of OXY in comparison to Oxytrol®.

The Phase 3 clinical efficacy and safety study (Study OG05009) was conducted using 1 g sachet of the 10% OTG (Sachet Code # 0599). The to-be-marketed product has the same composition as the product used in the pivotal Phase 3 study.

2.6 Analytical Section

Plasma samples were analyzed for racemic and enantiomeric OXY and DEO concentrations by (b) (4) using a high performance liquid chromatography-tandem mass spectroscopy method. The analytical method was developed and validated by (b) (4)

according to Standard Operating Procedures that were written based on Good Laboratory Practices (GLP) guidelines described in 21 CFR Part 58 and the FDA Guidance for Industry - Bioanalytical Method Validation (CDER, May 2001). No bioanalytical analyses were performed at (b) (4) Canadian sites for any study.

An aliquot of human plasma containing each analyte and internal standard was extracted using a solid-phase extraction procedure. The extracted samples were analyzed by a mass spectrometer. Quantitation was by peak area ratio. Positive ions were monitored in the multiple reaction monitoring mode. Human plasma (EDTA), free of significant interference, was used to prepare calibration standard and quality control samples.

The lower limit of quantitation (LLOQ) of the R- and S-oxybutynin and R- and S-DEO assays was 0.05 ng/mL. Sample concentrations that calculated below the LOQ were reported as <0.05 ng/mL (or as appropriate for the dilution). Quality control and standard samples were included with each drug assay run to provide within study validation of assay performance and for calculation of study sample concentrations. High and low concentration quality control samples were analyzed concurrently with the subject samples.

Blood samples were processed according to standard procedures at the clinic. The resulting plasma fractions were isolated, split into equal aliquots, and transferred to labeled, leak-proof tubes. The tubes had tops that were securely fastened before being transferred and stored in a -20°C freezer. (b) (4)

A set of at least nine OXY and DEO calibration standards (0.05, 0.10, 0.20, 0.50, 1.00, 2.00, 5.00, 8.00, 10.00 ng/mL) and three sets of quality control standards (0.15, 1.50, and 7.50 ng/mL) were used for analysis. For OXY and DEO, the sponsor evaluated the following stability properties:
Long-term stability: 83 weeks at -20°C
Short-term stability: 25 hours at room temperature under non-UV filtered light
Freeze-thaw stability: 6 cycles
Processed sample integrity: 314 hours in glass injection vials with plastic inserts
Post-preparative stability: 72 hours

Standards were rejected if they were greater than + 15% for all standards but the LLOQ or 20% for LLOQ standards.

The bioanalytical method was validated and is acceptable. All methods met the FDA recommended acceptance criteria of $\leq$20% for precision (CV) and within $\pm$20% for accuracy at the LLOQ and $\leq$15% at all other concentrations.

3 Detailed Labeling Recommendations

(1) Under the Pharmacokinetics Geriatrics Section, the sponsor states the following:

(b) (4)

The use of the term (b) (4) is vague and suggests that the effect in geriatrics was methodically evaluated during the clinical study. This reviewer proposes to replace (b) (4) with "no significant differences".

(2) The following figure is the plasma concentration vs. time profile for OXY at steady state from Section 12.2 Pharmacokinetics of the sponsor's proposed label. The plasma concentration is expressed as a mean ± SEM; this reviewer recommends having concentration expressed as mean ± SD.

(b) (4)

(3) The sponsor proposed to include a (b) (4)® in their label. This reviewer recommends (b) (4) comparing (b) (4)

(b) (4)

Appendices

Individual Study Reviews

Study OG03005

Title: An evaluation of the single and multiple dose pharmacokinetics of oxybutynin and N-desethyloxybutynin following administration of 3 gm (of 4.4%) oxybutynin gel in healthy volunteers.

Objective: The primary objective was to evaluate the single and multiple dose pharmacokinetics of OXY and DEO following application of 3 gm of 4.4% OTG in healthy male and female subjects. The secondary objective was to evaluate the safety of the gel formulation based on skin tolerability, electrocardiogram, blood pressure and occurrence of adverse events.

Methods: The study was a two period, open-label, multiple dose study design to evaluate the single and multiple dose pharmacokinetics and safety of 3 gm of 4.4% OTG following application on the abdomen. The total study duration was approximately 19 days with the first treatment period consisting of a 2-day inpatient phase and a 1-day outpatient phase that included a single gel application followed by serial blood sampling for approximately 72 hours. A 7-day washout immediately followed the first application. The second treatment period consisted of applying the gel for 7 consecutive days to rotating sites on the abdomen, upper arms/shoulders and thighs. Subjects were confined to the clinic from the evening of the 6^{th} dose for approximately 2.5 days. There were twenty subjects who enrolled and completed the study (11 male and 9 female subjects). The mean (SD) age is 24.2 (6.15) years with a range of 20 to 44 years. The weight (SD) and BMI (SD) were 72.5 (12.82) kg and 24.2 (2.43) kg/m^2, respectively. One subject was Asian, one African-American, and the remaining 18 were Caucasian.

Pharmacokinetic Sampling: Blood samples were collected daily for determination of OXY and DEO plasma concentrations before each application and serially after the final application of OTG. After the first dose, blood samples were drawn 30 minutes prior to the first dose, and at 2, 4, 8, 12, 16, 20, 23, 24, 26, 28, 32, 36, 40, 44, 48, and 72 hours. Samples were also drawn immediately prior to each gel application on Days 9-15 and at 2, 4, 8, 12, 16, 20, 23, 24, 26, 28, 32, 36, 40, 44, 48, and 72 hours after the Day 15 dose.

Results:

The 4.4% OTG was the first gel formulation developed to approximate the daily delivery of 39 cm^2 Oxytrol®. The sponsor states that results from initial *in vitro* studies using human cadaver skin models suggested that approximately 3 gm of 4.4% gel would achieve comparable plasma oxybutynin levels as compared to Oxytrol®. The sponsor showed that this formulation and dose may deliver comparable, as detemined by average daily plasma concentration, oxybutynin as the Oxytrol® transdermal system

The table below shows a summary of OXY and DEO PK parameters after a single dose of 3 gm of 4.4% OTG. There was high variability in AUC_{0-72} (%CV were 32.52 and 39.64 for OXY and DEO, resp.) and C_{max} (%CV were 54.82 and 37.67 for OXY and DEO, resp.). The high variability in C_{max} can be explained in part by subjects 209 and 211 who had a large and sudden spike in the OXY level around 24 hrs post dose. The mean T_{max} for OXY and DEO were similar at 24.00 and 26.00 hrs, respectively. There was a significant difference in the $t_{1/2}$ (18.18 hrs for OXY versus 45.84 hrs for DEO) as would be expected since DEO is the metabolite of OXY and would be slowly generated following topical delivery of oxybutynin. C_{max} of 6.35 ng/mL was reached with a median T_{max} of 24 hrs.

Based on the multiple dose study, the mean (SD) average plasma concentration (C_{avg}) of OXY during the 20 hours following the final application of 3 gm of 4.4% OTG was 6.22 (2.00) ng/mL. According to the Oxytrol® label and based on AUC_{0-96}, the C_{avg} for oxybutynin is 4.2 (1.1) ng/mL. Though not exactly the same, this cross study comparison seem to suggest that 3 gm of 4.4% OTG would provide comparable

average plasma concentrations of OXY from OTG and Oxytrol®. The elimination half-life was approximately 24 hours during the 48 hours following the final dose.

Table. Summary of single dose OXY and DEO mean (SD) PK parameters following 3 gm of 4.4% OTG.

	3 gm of 4.4% OTG	
Parameter	OXY	DEO
AUC_{0-24} (ng·hr/mL)	64.27 (28.11)	50.26 (24.01)
AUC_{0-72} (ng·hr/mL)	185.65 (60.37)	157.35 (62.38)
AUC_{0-72} DEO:OXY	0.87 (0.27)	
C_{max} (ng/mL)	6.35 (3.48)	4.50 (1.69)
T_{max} (hr)	26.70 (8.65)	27.05 (6.17)
$T_{1/2}$ (hr)	18.18 (6.91)	45.84 (123.68)

Figure. Mean ± SEM plasma OXY and DEO plasma concentrations following a single 3 gm dose of 4.4% OTG.

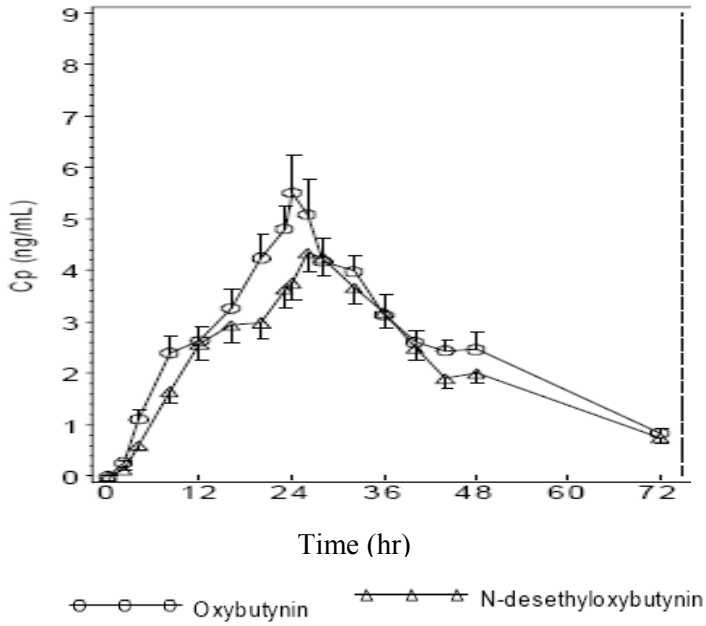


Table. Summary of multiple dose OXY and DEO mean (SD) PK parameters following the final dose of multiple doses of 3 gm of 4.4% OTG.

	3 gm of 4.4% OTG	
Parameter	OXY	DEO
AUC_{0-24} (ng·hr/mL)	149.30 (48.05)	125.39 (42.75)
AUC_{0-24} DEO:OXY	0.87 (0.27)	
C_{avg} (ng/mL)	6.22 (2.00)	5.22 (1.78)
C_{max} (ng/mL)	9.01 (3.36)	6.44 (2.14)
T_{max} (hr)	20.90 (5.68)	14.75 (9.67)
$T_{1/2}$ (hr)	23.87 (14.52)	33.39 (24.22)

Figure. Mean ± SEM plasma OXY and DEP concentrations following multiple dose administration of 3 gm dose of 4.4% OTG.

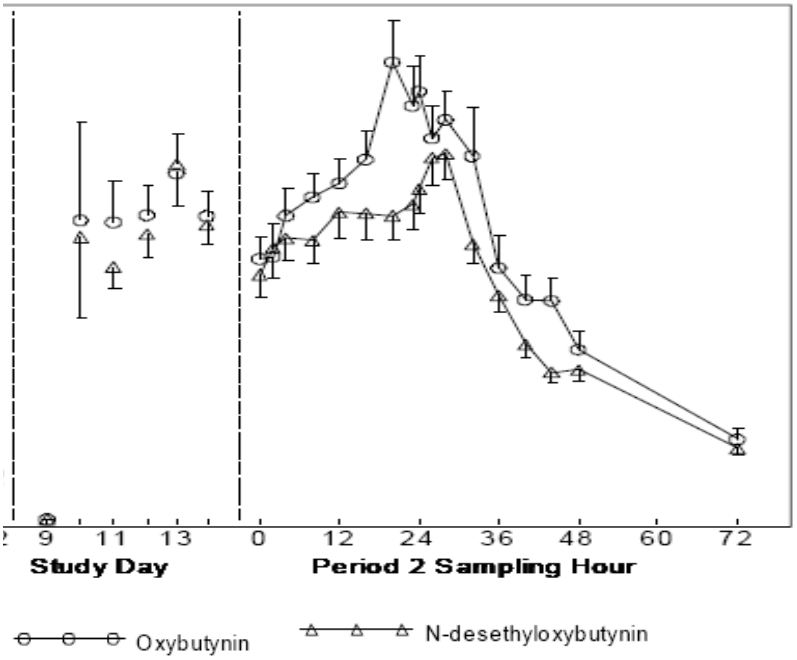


Table. Summary of trough OXY and DEO concentrations (SD) prior to dosing during multiple dose treatment period.

Application Day and Site	OXY (ng/mL)	DEO (ng/mL)
Day 10 – abdomen	5.31 (7.75)	5.02 (6.46)
Day 11 – shoulder	5.28 (3.30)	4.48 (1.72)
Day 12 – thigh	5.40 (2.30)	5.08 (1.90)
Day 13 – abdomen	6.15 (2.62)	6.31 (2.32)
Day 14 – shoulder	5.39 (1.96)	5.24 (1.60)
Day 15 – thigh	4.63 (1.71)	4.36 (1.83)

Study OG04007

Title: Single dose pharmacokinetics of oxybutynin and metabolites following transdermal application of 39 cm^2 Oxytrol® transdermal system, 3 gm of 4.4% topical oxybutynin gel, 1 gm of 10% topical oxybutynin gel and 3 gm of 10% topical oxybutynin gel in healthy volunteers.

Objective: The primary objective was to evaluate and compare the pharmacokinetics and metabolism of oxybutynin administered as a single dose of 39 cm^2 Oxytrol®, 3 gm of 4.4% of OTG, 1 gm of 10% OTG, and 3 gm of 10% OTG. The secondary objectives were to estimate the volume of gel required to achieve plasma concentrations similar to that achieved with a single application of 39 cm^2 Oxytrol® and to assess local skin tolerability of the three topical preparations. This study was one of the most critical for this NDA as it was a relative bioavailability study to demonstrate comparable systemic exposure of oxybutynin from the transdermal patch and several formulations of the topical gel, including the to-be-marketed formulation.

Methods: The study was a single dose, four-period, open-label, randomized, crossover design comparing 39 cm^2 Oxytrol® patch and three different doses/formulations of oxybutynin topical gel (3 gm of 4.4% OTG, 1 gm of 10% of OTG, and 3 gm of 10% of OTG). Twenty-two subjects (13 males and 9 females) were enrolled in the study; however only twenty subjects completed all four treatment periods of the study. The mean (SD) age was 26.4 (7.49) years with a range from 18 to 45 years. Most subjects (18) were Caucasian, 3 Hispanic, and 1 multiracial. The gel was applied on the abdomen by the subject with their own hand. The subjects were instructed to wash the hand with soap and warm water within 5 minutes of application. For the Oxytrol® group, the patch was applied to the abdomen of each subject by a clinic personal.

Pharmacokinetic Sampling: Blood samples for plasma concentrations of OXY and DEO were taken within 30 minutes prior to the first dose, and at approximately 2, 6, 12, 16, 24, 28, 32, 36, 44, 48, 52, 56, 72, 84, 96, 120, and 144 hours after each dose.

Results:

In order to minimized the application volume while maintaining the same amount of drug absorbed, Watson developed a more concentrated gel formulation (10%) and estimated that approximately 1.5 gm of 10% gel would match the blood concentration obtained from the previously evaluated 3 gm of 4.4% gel formulation. In study OG04007, Watson evaluated single dose PK of oxybutynin and N-desethyloxybutynin following transdermal application of 39 cm^2 Oxytrol®, 3 gm of 4.4% OTG, 1 gm of 10% OTG, and 3 gm of 10% OTG. The following tables summarize selected PK parameters for oxybutynin and N-desethyloxybutynin following administration of Oxytrol and the different oxybutynin topical gel formulations.

As expected, the AUC for OXY and DEO is significantly higher for the twice weekly dosing of Oxytrol compared to the daily dosing of OTG. However, the $t_{1/2}$ for OXY and DEO was longer for OTG (31.6 and 28.1 hrs) compared to Oxytrol (18.1 and 19.1 hrs).

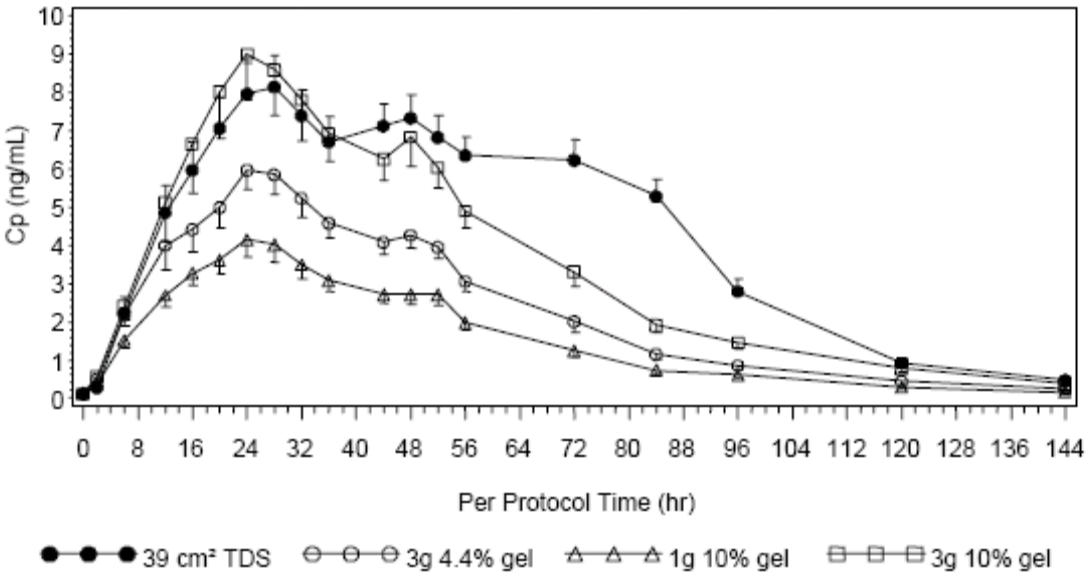
Table. Summary of OXY PK parameters following 3.9 mg/day Oxytrol®, 3 gm of 4.4% OTG, 1 gm of 10% OTG, and 3gm of 10% OTG. N=20 (Study OG04007)

Parameter Mean (SD)	Oxytrol® 39 cm^2	OTG 3 gm of 4.4%	OTG 1 gm of 10%	OTG 3 gm of 10%
AUC_{0-144} (ng·hr/mL)	295.69 (87.78)	172.84 (52.40)	116.17 (39.47)	275.18 (119.62)
C_{max} (ng/mL)	4.53 (1.63)	3.76 (1.43)	2.63 (1.02)	5.97 (3.25)
T_{max} (hr)	37.20 (17.70)	28.40 (11.60)	27.60 (10.21)	34.00 (15.87)
Ke (hr^{-1})	0.04 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
$T_{1/2}$ (hr)	18.09 (3.49)	26.93 (7.64)	31.62 (19.43)	27.41 (8.33)

Table. Summary of DEO PK parameters following 3.9 mg/day Oxytrol®, 3 gm of 4.4% OTG, 1 gm of 10% OTG, and 3gm of 10% OTG. N=20 (Study OG04007)

Parameter	Oxytrol® 39 cm^2	OTG 3 gm of 4.4%	OTG 1 gm of 10%	OTG 3 gm of 10%
AUC_{0-144} (ng·hr/mL)	318.71 (155.93)	152.18 (70.31)	103.29 (48.64)	223.73 (106.91)
AUC_{0-144} DEO:OXY	1.06 (0.36)	0.88 (0.32)	0.90 (0.35)	0.85 (0.36)
C_{max} (ng/mL)	4.48 (2.18)	2.88 (1.32)	2.15 (1.04)	4.18 (2.69)
T_{max} (hr)	39.40 (16.78)	31.80 (12.41)	30.40 (13.94)	32.60 (12.05)
Ke (hr^{-1})	0.04 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
$T_{1/2}$ (hr)	19.07 (5.54)	27.49 (7.57)	28.09 (9.35)	26.50 (9.72)

Figure: Mean plasma concentration vs. time profile for OXY + DEO following administration of each treatment (adopted from the sponsor's study report figure 11-5)



To select one of the three gel doses that would closely approximate the systemic exposure of OXY and DEO from 39 cm^2 Oxytrol®, the sponsor (1) estimated the exposure for once daily application of Oxytrol® and (2) modeled each gel profile and compared it to the recommended dosing of 1 Oxytrol® patch every 3.5 days.

Table: Dose-normalized OXY + DEO AUC_{0-144} for 39 cm^2 Oxytrol® and individual OTG treatments (adopted from the sponsor's study report table 11-6)

Parameter	Statistic	39 cm² TDS	3g 4.4% gel	1g 10% gel	3g 10% gel
Dose-Normalized AUC[0-144] (ng·hr/mL)	Mean (SD)	175.54 (65.77)	325.02 (110.92)	219.46 (78.51)	498.92 (212.43)
	SEM	14.71	24.80	17.56	47.50
	CV (%)	37.47	34.13	35.78	42.58
	Min, Max	89.23, 313.88	206.69, 612.36	118.16, 414.90	240.61, 1178.35
	n	20	20	20	20

Source: Table 14.2.2-3, Listings 16.2.6-1, 2

The approved dosing regimen for Oxytrol® is 1 patch applied twice weekly (every 3.5 days). In order to compare Oxytrol® applied twice weekly to daily application of the topical gel, the sponsor calculated a dose-normalized AUC for Oxytrol® by dividing the AUC_{0-144} by 3.5 days. The sponsor attempted to demonstrate that a single dose of 1 gm of 10% OTG (AUC_{0-144} for OXY+DEO of 219.46 ng.hr/mL) was comparable to a single dose of 39 cm^2 Oxytrol® (AUC_{0-144} for OXY+DEO of 175.54 ng.hr/mL) after normalizing for 3.5 days dosing interval; however, dividing the AUC_{0-144} from Oxytrol® by 3.5 is not equivalent to AUC_{0-144} after daily dosing of OTG. To more appropriately compare the systemic exposure of OXY for both products, the sponsor should have measured and compared the AUC_{0-84} following application of Oxytrol® and 3.5 times the AUC_{0-24} following application of OTG then multiplying by 3.5.

Table: Summary of predicted steady-state PK parameters for OXY, DEO, and Oxy + DEO by treatment groups.

	C_{min} (ng/mL)			C_{max} (ng/mL)			C_{avg} (ng/mL)		
Treatment	OXY	DEO	OXY+DEO	OXY	DEO	OXY+DEO	OXY	DEO	OXY+DEO
Oxytrol® 39 cm^2	1.0	1.3	2.3	5.2	5.6	10.8	4.0	4.6	8.6
3 g 4.4% Gel	4.8	4.4	9.2	8.4	7.5	15.9	8.0	7.2	15.2
1 g 10% Gel	3.2	3.1	6.3	5.7	5.2	10.9	5.4	5.0	10.4
3 g 10% Gel	7.9	6.9	14.8	13.7	11.2	24.9	13.1	10.9	24.0

The measured single dose plasma concentration data were used to generate PK parameter for each treatment. Simulations using selected output parameter were then used to simulate plasma concentration profiles for 14 days of daily dosing of the gel and every 84 hours for Oxytrol. From the above table, the simulations suggest that daily dosing of 1 gm of 10% OTG (C_{avg} for OXY+DEO 10.4 ng/mL) would provide comparable steady-state plasma concentration profiles to every 3.5 day dosing of 39 cm^2 Oxytrol® (C_{avg} for OXY+DEO 8.6 ng/mL). The C_{avg} for OXY and DEO for 1 gm of 10% OTG was most comparable to Oxytrol®.

Of all the doses and formulations tested, the 1 gm of 10% OTG achieved the most comparable systemic exposure for OXY+DEO to 39 cm^2 Oxytrol. The simulated steady state model also suggests that the multiple doses of 1 gm of 10% OTG would match steady-state conditions with Oxytrol®.

Study OG04008

Title: Multiple dose pharmacokinetics and relative bioavailability of racemic oxybutynin, R and S enantiomers and metabolites following application of 10% oxybutynin gel to the abdomen, upper arms and thighs of healthy volunteers.

Objective: The primary objective was to evaluate, based on racemic OXY and DEO concentrations, the relative bioavailability of 1 gm of 10% topical gel oxybutynin following applications to the abdomen, upper arms/shoulder and thigh. The secondary objectives were to evaluate and compare the pharmacokinetics and metabolism of OXY and its enantiomers when administered as a gel to the different areas of the body and to assess the local skin tolerability at each site.

Methods: The study was a multiple dose, three period, open-label, randomized, crossover design comparing the relative bioavailability and steady state pharmacokinetics of OXY, DEO, and enantiomers following gel application to the abdomen, upper arm/shoulder and thigh. The subjects were dosed with 1 gm of 10% OTG for 42 days (14 days of treatment for each application site with no washout period before rotating to the next application site). For each application site treatment period, subjects received 13 days of outpatient gel applications followed by one day of inpatient gel application (on Days 14, 28, and 42). There were forty healthy (20 male and 20 female) volunteers enrolled, but thirty-nine completed all three treatment periods. The mean (SD) age of the subjects was 25.7 (6.78) years with a range of 28 to 45 years. Five were African-American and the rest were Caucasian.

Pharmacokinetic Sampling: On 14th day of each treatment period, subjects returned to the clinic for 24 hours of inpatient serial blood sampling. Following the final gel application in the third treatment period, subjects had 6 additional outpatient visits for single daily blood samples, which provided the PK profile for all three treatment arms from Days 42-49. Blood samples were taken for plasma concentrations of R and S OXY and R and S DEO and were taken within 30 minutes prior to the first inpatient dose, and at approximately 2, 4, 6, 8, 12, 16, 20, and 24 hours after the dose.

Results:

The mean plasma concentration for OXY and DEO fluctuated minimally following during the 24 hour dosing interval following 14 days of OTG daily application and were similar at the abdomen, thigh and upper arm/shoulder. The profiles for OXY and DEO were fairly flat for all three application sites with the mean C_{avg} for OXY ranging from 4.7 to 5.5 ng/mL. Based on the label for Oxytrol®, the mean (SD) C_{avg} for OXY following multiple dosing was 4.2 (1.1) ng/mL.

Figure: Mean (±SEM) OXY plasma concentrations following application of 1 gm of 10% OTG to the abdomen, upper arm/shoulder and thigh (adopted from the sponsor's study report figure 11-1)

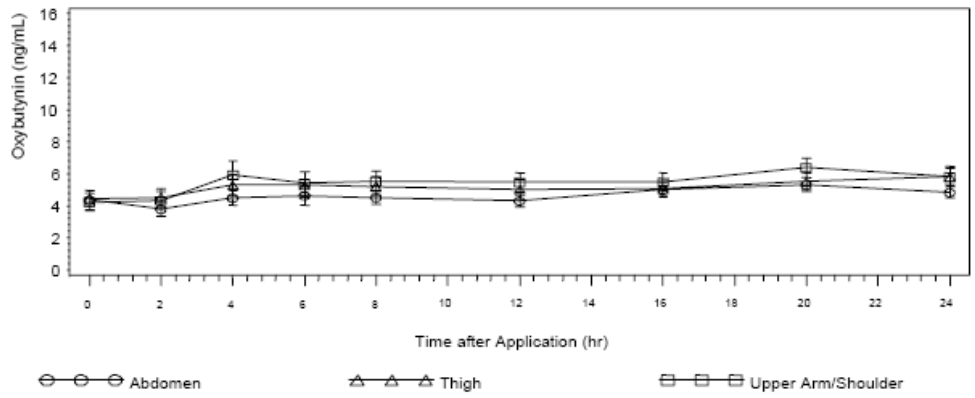


Figure: Mean (±SEM) DEO plasma concentrations following daily application of 1 gm of 10% OTG to the abdomen, upper arm/shoulder and thigh for 14 days (adopted from the sponsor's study report figure 11-2)

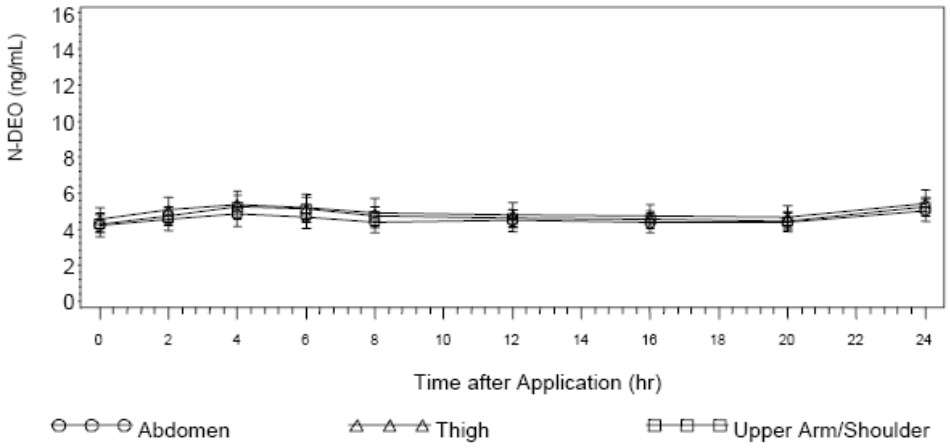


Table adopted from approved Oxytrol® label.

Table 1: Mean (SD) oxybutynin pharmacokinetic parameters from single and multiple dose studies in healthy men and women volunteers after application of **OXYTROL** on the abdomen.

Dosing	**Oxybutynin**			
	C_{max} (SD) (ng/mL)	T_{max} [1] (hr)	C_{avg} (SD) (ng/mL)	AUC (SD) (ng/mLxh)
Single	3.0 (0.8)	48	—	245 (59) [2]
	3.4 (1.1)	36	—	279 (99) [2]
Multiple	6.6 (2.4)	10	4.2 (1.1)	408 (108) [3]
	4.2 (1.0)	28	3.1 (0.7)	259 (57) [4]

Following the final application of OTG of the third treatment period, plasma concentrations of OXY, DEO, and OXY+DEO were measured for 7 consecutive days to characterize the elimination of OXY and DEO in 37 of the 39 subjects who completed the study, regardless of application site. In the figure below, the elimination following 24 hours of the final dose and up to 72 hours decreased steadily followed by a more gradual elimination to the final sampling time (168 hrs) with OXY and DEO concentration was 0.24 and 0.26 ng/mL, respectively. Based on the single dose PK study with elimination half-life for OXY and DEO at 31.6 and 28.1 hrs, respectively, complete elimination would be expected at approximately 150 hrs (5 times $t_{1/2}$ of ~30 hrs). At 168 hours, the elimination of OXY and DEO following multiple dosing is nearly complete as one would predict from the single dose PK study.

Figure: Mean (+SEM) OXY, DEO, and OXY+DEO Concentrations for Days 42-49 (adopted from the sponsor's study report figure 11-3)

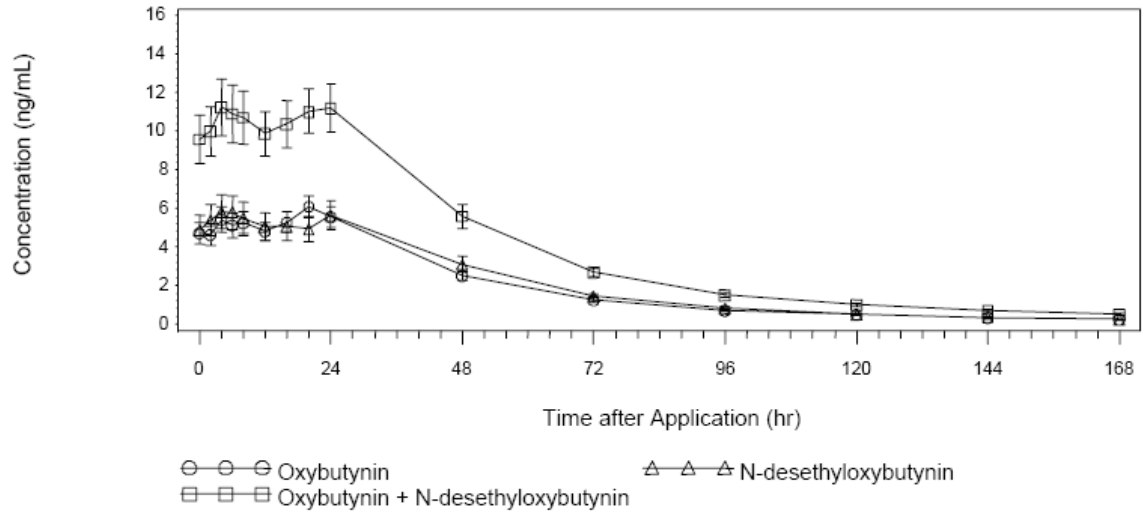


Table: Summary of PK parameters for OXY following daily application of 1 gm of 10% OTG to the abdomen, thigh, and upper arm/shoulder for 14 days (adopted from the sponsor's study report table 11-2)

Parameter	Statistic	Abdomen	Thigh	Upper Arm/Shoulder
$AUC_{[0-24]}$ (ng·hr/mL)	Mean (SD)	112.69 (57.997)	125.12 (84.674)	133.78 (81.578)
	CV (%)	51.47	67.67	60.98
	Min, Max	16.11, 268.90	22.16, 395.11	16.40, 373.45
C_{max}(ng/mL)	Mean (SD)	6.77 (3.933)	6.97 (4.949)	8.26 (5.972)
	CV (%)	58.09	71.00	72.26
	Min, Max	0.94, 21.70	1.71, 25.00	1.00, 31.50
C_{avg} (ng/mL)	Mean (SD)	4.66 (2.395)	5.18 (3.503)	5.54 (3.375)
	CV (%)	51.39	67.64	60.94
	Min, Max	0.67, 10.98	0.90, 16.21	0.68, 15.24
C_{min}(ng/mL)	Mean (SD)	3.27 (2.157)	3.84 (2.829)	3.49 (2.352)
	CV (%)	65.98	73.62	67.35
	Min, Max	0.00, 9.96	0.15, 13.72	0.05, 12.00
T_{max}(hr)	Mean (SD)	13.14 (8.370)	13.53 (9.075)	13.53 (8.210)
	Median	16.00	16.00	16.00
	Min, Max	-0.50, 24.00	-0.50, 24.00	-0.50, 24.00

Table: Summary of mean (SD) steady-state PK parameters for OXY following application of 1 gm of 10% OTG to the abdomen, thigh, and upper arm/shoulder (adopted from the sponsor's study report table 11-2 (modified))

Application Site	AUC_{0-24} (ng.hr/mL)	C_{max} (ng/mL)	C_{avg} (ng/mL)
Abdomen	112.7 (58.00)	6.8 (3.93)	4.7 (2.39)
Upper Arm/Shoulder	133.8 (81.58)	8.3 (5.97)	5.5 (3.37)
Thigh	125.1 (84.67)	7.0 (4.95)	5.2 (3.50)

Table: Summary of PK parameters for DEO following application of 1 gm of 10% OTG to the abdomen, thigh, and upper arm/shoulder (adopted from the sponsor's study report table 11-3)

Parameter	Statistic	Abdomen	Thigh	Upper Arm/Shoulder
$AUC_{[0-24]}$	Mean (SD)	109.31 (87.385)	118.81 (104.604)	114.10 (75.770)
(ng·hr/mL)	CV (%)	79.94	88.04	66.41
	Min, Max	9.85, 518.65	21.07, 644.22	15.97, 374.78
C_{max}(ng/mL)	Mean (SD)	5.44 (3.969)	6.12 (5.109)	6.07 (4.102)
	CV (%)	72.92	83.55	67.59
	Min, Max	0.68, 22.85	1.14, 31.50	0.81, 19.45
C_{avg} (ng/mL)	Mean (SD)	4.52 (3.588)	4.92 (4.351)	4.73 (3.148)
	CV (%)	79.41	88.44	66.60
	Min, Max	0.41, 21.17	0.88, 26.84	0.67, 15.62
C_{min}(ng/mL)	Mean (SD)	3.67 (3.310)	4.07 (3.865)	3.68 (2.417)
	CV (%)	90.08	95.03	65.60
	Min, Max	0.00, 19.08	0.12, 23.60	0.41, 11.63
T_{max}(hr)	Mean (SD)	14.18 (9.909)	14.51 (9.881)	14.72 (9.974)
	Median	16.00	20.00	24.00
	Min, Max	-0.50, 24.00	2.00, 24.00	0.00, 24.00

Table: Application site bioequivalence assessment for OXY and DEO (adopted from the sponsor's study report table 11-5)

Variable	Comparison (Test:Reference)	PK Parameter	Ratio	90% Confidence Interval	Bioequivalence Achieved?
Oxybutynin	Thigh: Abdomen	$AUC_{[0-24]}$	1.07	0.93,1.23	YES
		C_{max}	0.99	0.85,1.16	YES
	Arm:Abdomen	$AUC_{[0-24]}$	1.14	0.99,1.31	NO
		C_{max}	1.14	0.97,1.33	NO
DEO	Thigh: Abdomen	$AUC_{[0-24]}$	1.09	0.95,1.26	NO
		C_{max}	1.11	0.96,1.28	NO
	Arm:Abdomen	$AUC_{[0-24]}$	1.09	0.94,1.25	NO
		C_{max}	1.13	0.98,1.30	NO

Statistical analyses of the AUC and Cmax parameters comparing application sites showed OXY absorption at all three sites to be similar, but only strictly bioequivalent between the thigh and abdominal sites based on the 90% confidence intervals for OXY. DEO concentrations were not bioequivalent between thigh and abdominal sites, or for the upper arm/shoulder and abdomen for either PK parameters.

The PK parameters for the R and S enantiomers were similar between applications sites. Plasma concentrations of S-OXY (AUC_{0-24}) were approximately 20% higher than R-OXY concentrations, and conversely, R-DEO concentrations were approximately 25% higher than S-DEO concentrations.

Study OG06005

Title: A steady-state comparison of plasma oxybutynin, N-desethyloxybutynin and R and S enantiomer concentrations following multiple dose application of 1 G oxybutynin topical gel and Oxytrol® oxybutynin transdermal system in healthy volunteers.

Objective: The primary objective was to compare the steady-state pharmacokinetics and plasma concentrations of oxybutynin, N-desethyloxybutynin and the R and S enantiomers of oxybutynin and N-desethyloxybutynin following Oxybutynin Topical Gel (OTG) and Oxytrol Oxybutynin Transdermal System (TDS). The secondary objectives were to evaluate the local skin tolerability at the application sites of the two products and assess safety based on the occurrence of adverse events.

Methods: This study was a multiple dose, two period, open-label, randomized crossover design comparing steady-state plasma concentrations and pharmacokinetics of 1 gm of 10% OTG and Oxytrol® TDS. Each treatment period consisted of 18 days of treatment with either OTG (applied daily) applied to rotating sites on the abdomen, thighs, and upper arms or Oxytrol (applied four times every 3.5 days, followed by one 4-day application) applied to rotating sites on the abdomen, hip, and buttocks. Twenty-two subjects were enrolled in the study, but twenty subjects (12 males and 8 females) completed both treatment periods. The mean (SD) age was 25.4 (8.07) years with a range from 18 to 44 years. Most subjects (18) were Caucasian, 1 was African-American, and 1 was bi-racial (African-American and Caucasian).

Pharmacokinetic Sampling: In each dosing period blood samples were collected for analysis of R- and S- enantiomers of oxybutynin and DEO during the final 4 days of dosing (last application of Oxytrol TDS and the final 4 daily applications of OTG). Blood samples were drawn within 30 minutes prior to the first inpatient dose in each period, and at approximately 12, 24, 36, 48, 60, 72, 84, and 96 hours after the dose. The following PK parameters were characterized for OTG and Oxytrol: AUC_{0-96}, C_{max}, C_{avg}, and T_{max}.

Results:
During the final 4 days of dosing, the mean AUC_{0-96} for oxybutynin was 321.7 and 312.5 ng.hr/mL for OTG and Oxytrol TDS, respectively, which represents an insignificant (2.94%) higher exposure from OTG. The mean C_{avg} for oxybutynin delivered from OTG and Oxytrol TDS was very similar at 3.35 and 3.26 ng/mL, respectively.

Based on the product label for Oxytrol®, the mean (SD) C_{avg} for OXY following multiple dosing was 4.2 (1.1) ng/mL. The mean (SD) C_{avg} for OXY for OTG was 3.35 (1.17) ng/mL, which is comparable to that observed with multiple doses of Oxytrol®; however, the number of blood samples taken to determine AUC_{0-96} and C_{avg} were sparse. There were only 9 blood samples taken over the 96 hour period (1 sample every 12-hour interval). In the study to assess bioavailability at different application sites (Study OG04008) where the PK parameters where calculated based on 8 blood samples taken over a 24 hour time frame, the AUC_{0-24} (average of the three sites) was 123.9 ng.hr/mL and C_{avg} ranged from 4.7 to 5.5 ng/mL.

Extrapolating AUC_{0-24} over a 96 hour period with more frequent blood draws, the AUC_{0-96} is expected to be approximately 495.6 ng.hr/mL (not 321.7 ng.hr/mL) so it appears that the infrequent sampling over the 96 hour period in this multiple dose study may have resulted in an under-estimation of the AUC_{0-96} and C_{avg}. Additionally, in this study, one of nine blood samples was not obtained from Subjects 1306 and 1309 following OTG application and one of nine blood samples was not obtained from Subjects 1307 and 1317 after Oxytrol® application which may have also contributed to the under-estimation of AUC_{0-96} and C_{avg}. It is the opinion of this reviewer that PK parameters determined from Study OG06005 does not accurately reflect the steady state plasma concentration vs. time profile for OXY and DEO following

multiple applications of OTG and Oxytol® due to infrequent sampling and should not be included in the product label.

For the active metabolite N-desethyloxybutynin, the mean AUC_{0-96} was significantly different with 246.4 and 338.0 ng.hr/mL for OTG and Oxytrol TDS, respectively. The mean C_{avg} was also significantly different with 2.57 and 3.52 ng/mL for OTG and Oxytrol TDS, respectively. The T_{max} was longer for OTG at 44.40 hours, compared to 35.40 hours for Oxytrol TDS. The AUC_{0-96} ratios of DEO:OXY was 0.77 and 1.07 for OTG and Oxytrol TDS, respectively. As evidenced by the pharmacokinetic information, the metabolism of oxybutynin to N-desethyloxybutynin was slightly greater following Oxytrol application. The sponsor believes that inhibition of CYP450 activity in the epidermis by (b) (4) from the Oxytrol formulation is likely responsible for the observed higher concentrations of DEO.

The mean AUC_{0-96} for R- and S-OXY enantiomers was very similar with 143.3 and 178.3 from OTG and 138.6 and 173.9 from Oxytrol TDS, respectively.

Along with Studies OG04008 and OG03005, this study provides additional support that at steady-state OTG delivers comparable levels of oxybutynin and is expected to perform similarly to Oxytrol TDS.

Figure: Mean ± SEM oxybutynin concentration vs. time profiles for OTG and TDS during 96-hour dosing period (adopted from the sponsor's study report figure 11-1)

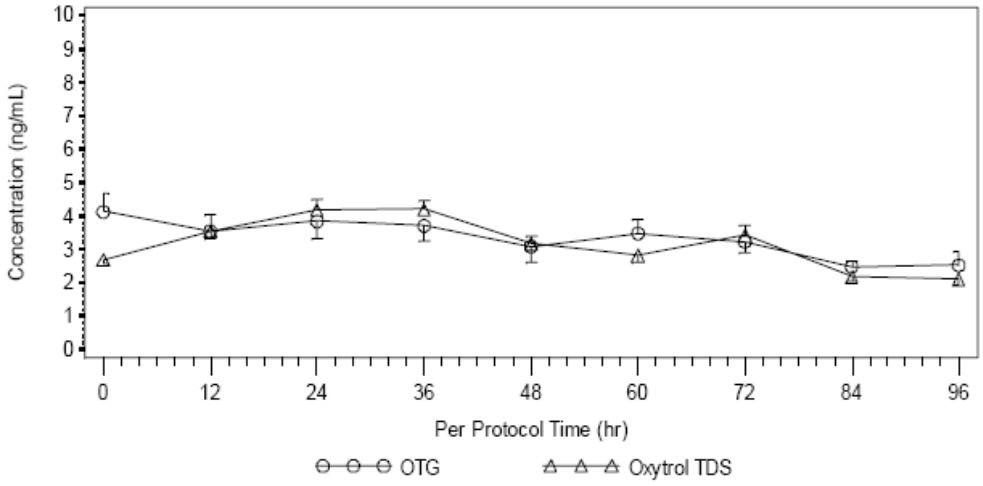


Table: Summary of oxybutynin pharmacokinetics for OTG and Oxytrol (adopted from the sponsor's study report table 11-2)

Parameter	Statistic	OTG N = 20	TDS N = 20
$AUC_{[0-96]}$	Mean (SD)	321.7 (112.3)	312.5 (67.62)
(ng·hr/mL)	SEM	25.12	15.12
	CV (%)	34.92	21.64
	Min, Max	146.8, 578.5	191.5, 430.0
C_{avg} (ng/mL)	Mean (SD)	3.35 (1.17)	3.26 (0.70)
	SEM	0.26	0.16
	CV (%)	34.92	21.64
	Min, Max	1.53, 6.03	1.99, 4.48
C_{max} (ng/mL)	Mean (SD)	5.99 (2.58)	4.82 (1.31)
	SEM	0.58	0.29
	CV (%)	43.13	27.15
	Min, Max	2.30, 10.20	2.35, 8.16
C_{min} (ng/mL)	Mean (SD)	1.78 (0.60)	1.77 (0.58)
	SEM	0.13	0.13
	CV (%)	33.54	32.48
	Min, Max	0.80, 3.65	0.74, 3.11
T_{max} (hr)	Mean (SD)	36.00 (33.04)	40.80 (23.49)
	SEM	7.39	5.25
	Median	30.00	36.00
	Min, Max	0.00, 96.00	12.00, 72.00

Figure: Mean ± SEM plasma concentration vs. time profile for DEO following application of OTG and Oxytrol® during 96-hour dosing period (adopted from the sponsor's study report figure 11-2)

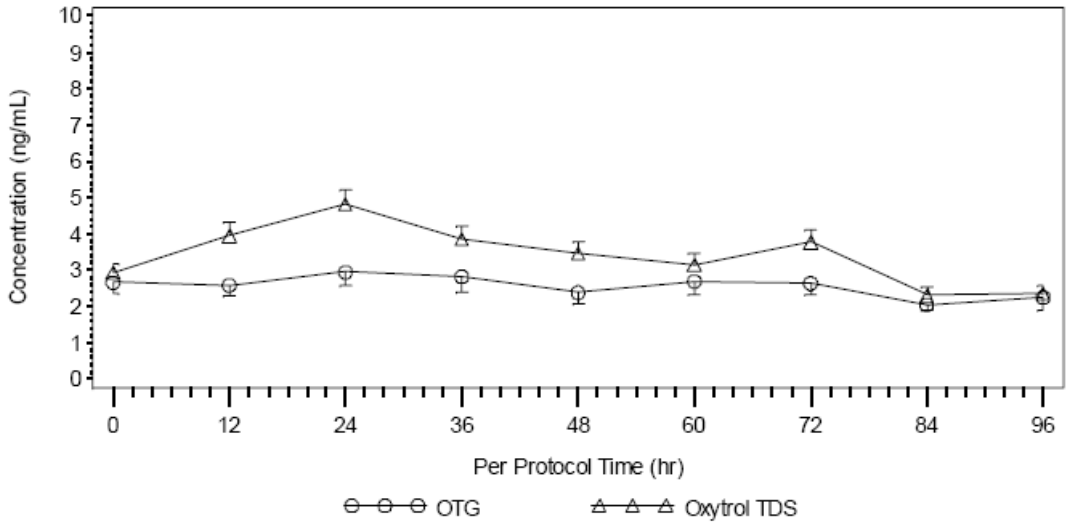


Table: Summary of mean (SD) PK for DEO following application of OTG and Oxytrol® (adopted from the sponsor's study report table 11-4)

Parameter	Statistic	OTG N = 20	TDS N = 20
$AUC_{[0-96]}$	Mean (SD)	246.4 (96.96)	338.0 (116.9)
(ng·hr/mL)	SEM	21.68	26.14
	CV (%)	39.36	34.60
	Min, Max	95.30, 462.0	151.2, 595.6
C_{avg} (ng/mL)	Mean (SD)	2.57 (1.01)	3.52 (1.22)
	SEM	0.23	0.27
	CV (%)	39.36	34.60
	Min, Max	0.99, 4.81	1.58, 6.20
C_{max} (ng/mL)	Mean (SD)	4.35 (2.30)	4.98 (1.68)
	SEM	0.52	0.38
	CV (%)	52.94	33.70
	Min, Max	1.39, 8.70	1.95, 8.50
T_{max} (hr)	Mean (SD)	44.40 (32.13)	35.40 (20.03)
	SEM	7.18	4.48
	Median	42.00	24.00
	Min, Max	0.00, 96.00	12.00, 72.00

Table: R- and S- oxybutynin mean (SD) pharmacokinetics (adopted from the sponsor's study report table 11-7)

		OTG		TDS	
Parameter	Statistic	R-Oxy	S-Oxy	R-Oxy	S-Oxy
$AUC_{[0-96]}$	Mean (SD)	143.3 (47.86)	178.3 (65.04)	138.6 (29.66)	173.9 (39.78)
(ng·hr/mL)	SEM	10.70	14.54	6.63	8.90
	CV (%)	33.40	36.47	21.40	22.87
	Min, Max	65.25, 243.8	81.54, 334.7	84.14, 190.8	107.3, 249.9
C_{avg} (ng/mL)	Mean (SD)	1.49 (0.50)	1.86 (0.68)	1.44 (0.31)	1.81 (0.41)
	SEM	0.11	0.15	0.07	0.09
	CV (%)	33.40	36.47	21.40	22.87
	Min, Max	0.68, 2.54	0.85, 3.49	0.88, 1.99	1.12, 2.60
C_{max} (ng/mL)	Mean (SD)	2.67 (1.14)	3.32 (1.46)	2.11 (0.58)	2.72 (0.73)
	SEM	0.26	0.33	0.13	0.16
	CV (%)	42.71	44.04	27.30	26.85
	Min, Max	1.01, 4.67	1.27, 5.74	1.08, 3.65	1.36, 4.51
C_{min} (ng/mL)	Mean (SD)	0.81 (0.24)	0.97 (0.35)	0.79 (0.23)	0.98 (0.36)
	SEM	0.05	0.08	0.05	0.08
	CV (%)	29.67	35.81	28.74	37.25
	Min, Max	0.44, 1.51	0.36, 2.05	0.33, 1.23	0.40, 1.88
T_{max} (hr)	Mean (SD)	34.80 (32.08)	36.00 (33.04)	41.40 (23.19)	37.80 (21.77)
	SEM	7.17	7.39	5.19	4.87
	Median	30.00	30.00	36.00	36.00
	Min, Max	0.00, 96.00	0.00, 96.00	12.00, 72.00	12.00, 72.00

Table: R- and S- N-desethyloxybutynin mean (SD) pharmacokinetics (adopted from the sponsor's study report table 11-8)

		OTG		TDS	
Parameter	**Statistic**	**R-DEO**	**S-DEO**	**R-DEO**	**S-DEO**
$AUC_{[0-96]}$	Mean (SD)	143.2 (45.88)	103.2 (56.97)	197.4 (74.68)	140.6 (63.96)
(ng·hr/mL)	SEM	10.26	12.74	16.70	14.30
	CV (%)	32.04	55.21	37.83	45.50
	Min, Max	60.62, 223.1	31.54, 239.0	88.84, 440.0	62.36, 317.2
C_{avg} (ng/mL)	Mean (SD)	1.49 (0.48)	1.07 (0.59)	2.06 (0.78)	1.46 (0.67)
	SEM	0.11	0.13	0.17	0.15
	CV (%)	32.04	55.21	37.83	45.50
	Min, Max	0.63, 2.32	0.33, 2.49	0.93, 4.58	0.65, 3.30
C_{max} (ng/mL)	Mean (SD)	2.51 (1.22)	1.86 (1.19)	2.96 (1.06)	2.06 (0.93)
	SEM	0.27	0.27	0.24	0.21
	CV (%)	48.47	64.03	35.72	45.40
	Min, Max	0.83, 5.15	0.52, 4.33	1.18, 5.98	0.79, 4.33
C_{min} (ng/mL)	Mean (SD)	0.86 (0.24)	0.61 (0.29)	1.19 (0.47)	0.85 (0.49)
	SEM	0.05	0.06	0.10	0.11
	CV (%)	27.86	47.47	39.33	58.33
	Min, Max	0.32, 1.23	0.18, 1.35	0.75, 2.48	0.18, 2.32
T_{max} (hr)	Mean (SD)	45.00 (31.36)	51.00 (30.38)	31.20 (17.15)	33.00 (22.66)
	SEM	7.01	6.79	3.83	5.07
	Median	42.00	54.00	24.00	24.00
	Min, Max	0.00, 96.00	0.00, 96.00	12.00, 72.00	0.00, 72.00

Study OG06001

Title: Plasma oxybutynin and N-desethyloxybutynin concentrations following application of 1 gm of 10% oxybutynin topical gel when co-administered with sunscreen lotion at the same application site.

Objective: The primary objective was to evaluate the effect of the application of sunscreen lotion on the rate and extent of absorption of oxybutynin when the sunscreen was applied either before or after applications of oxybutynin topical gel (OTG). The secondary objectives were to evaluate the effect of co-administration of OTG and sunscreen on the metabolism of oxybutynin, and to assess the safety of the combined application of the gel and sunscreen on the local tolerability at the application site and on the occurrence of adverse events.

Methods: This study was a single dose, three-period, open-label, randomized, crossover design. Subjects were assigned to receive 3 treatments (OTG alone, OTG preceded by sunscreen, and OTG followed by sunscreen) in a randomized sequence with each subject receiving each treatment once. The treatment interval was 32 days in duration and included 3 inpatient clinic visits for oxybutynin gel/sunscreen application and serial blood sampling followed by 2 outpatient clinic visits for single blood sample collections and a minimum of 14 days between each treatment period for washout. Each subject received 3 applications of 1 gm of 10% OTG applied by the subject to the abdomen with a predefined application area of 400 cm^2. Subjects also received so-administration of 800 mg of Coppertone® Oil-Free Sunblock Lotion Sun Screen Protection (SPF) 15 sunscreen lotion with OTG on 2 of the dosing days. Sixteen subjects enrolled in the study, but fourteen (6 males and 8 females) completed all three treatment periods. The mean (SD) age was 25.9 (6.71) years old with a range of 19 to 45. All subjects were Caucasian.

Pharmacokinetic Sampling: Blood samples for plasma concentrations of oxybutynin (OXY) and N-desethyloxybutynin (DEO) were taken 30 minutes prior to the first dose in each period, and at approximately 2,6, 12, 16, 20, 24, 28, 36, 48, and 72 hours after the dose.

Results:
The use of sunscreen either before or after application of topical oxybutynin gel did not affect the systemic exposure, pharmacokinetics, or metabolism of oxybutynin. The mean AUC_{0-72} for OTG alone, sunscreen before OTG, and sunscreen after OTG was 84.49, 91.15, and 83.55 ng.hr/mL, respectively. The mean C_{max} for all three treatment groups was very similar and ranged from 2.66 to 3.02 ng/mL, while the T_{max} was also similar with a range from 23.43 to 23.71 hour. The mean DEO:OXY ratio was also similar for all three groups and ranged from 0.78 to 0.82.

Skin tolerability as measured by the number of observed erythema was the absent from all sixteen subjects.

Figure: Mean (SEM) plasma concentration vs. time profile for oxybutynin and N-desethyloxybutynin following a 1 gm dose of 10% OTG (adopted from the sponsor's study report figure 11-1)

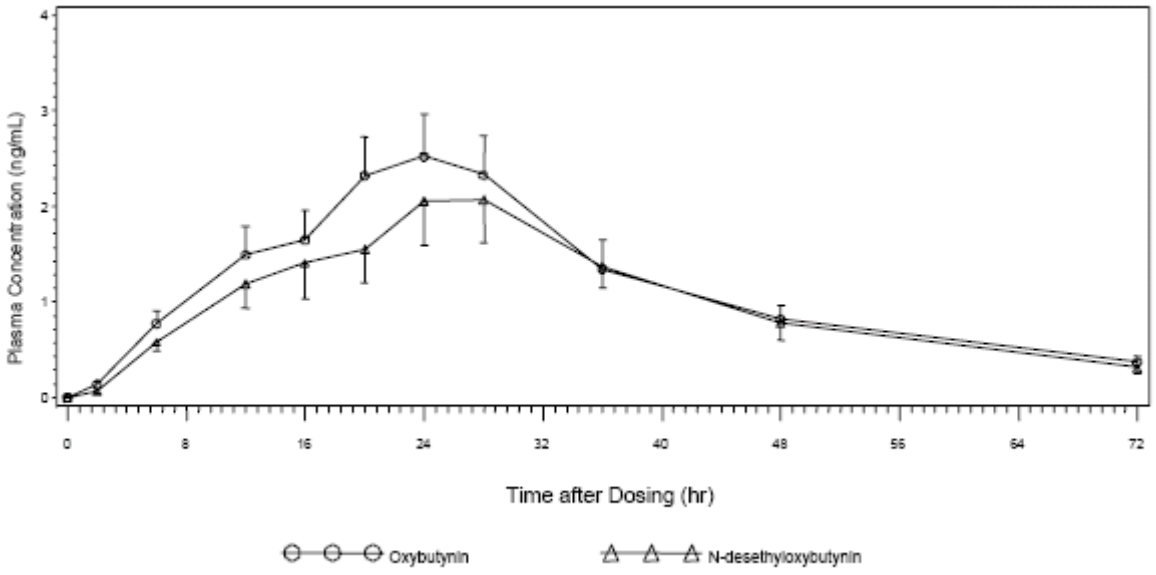


Figure: Mean (SEM) plasma concentration vs. time profile for oxybutynin and N-desethyloxybutynin after application of a 1 gm dose of 10% OTG following sunscreen application (adopted from the sponsor's study report figure 11-2)

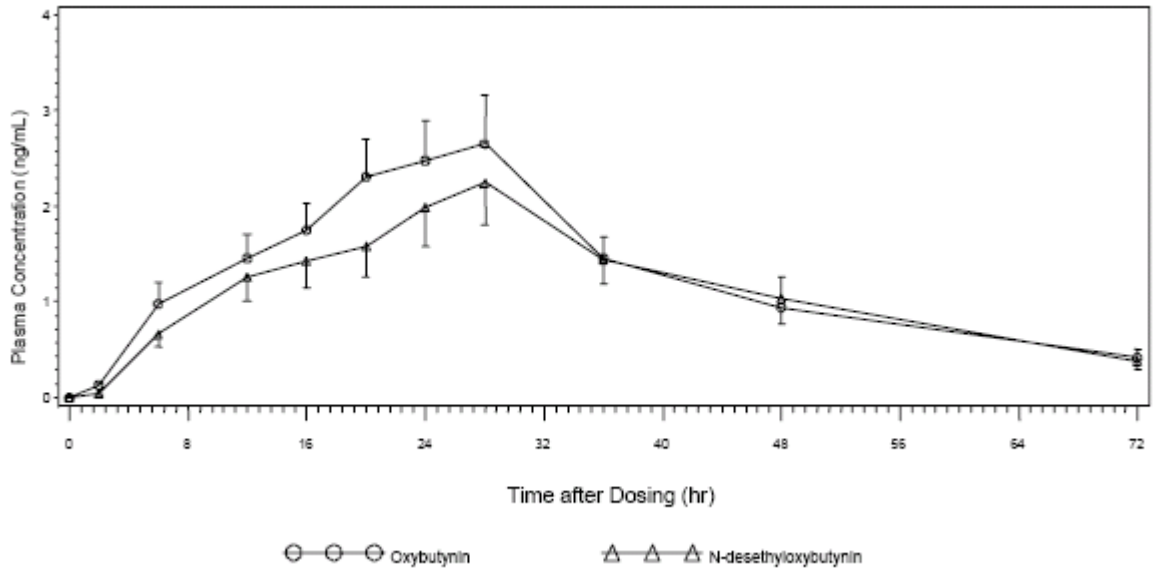


Figure: Mean (SEM) plasma concentration vs. time profile for oxybutynin and N-desethyloxybutynin after application of sunscreen followed by a 1 gm dose of 10% OTG (adopted from the sponsor's study report figure 11-3)

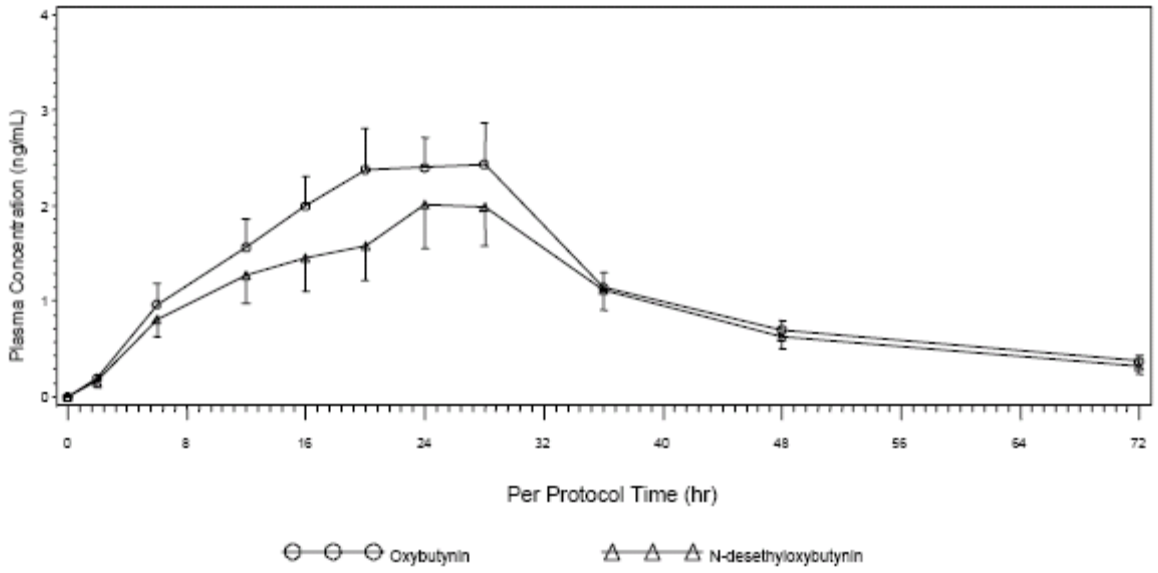


Table: Summary of pharmacokinetic parameters for oxybutynin by treatment regimen (adopted from the sponsor's study report table 11-2)

Parameter	Statistic	OTG Alone	Sunscreen/OTG	OTG/Sunscreen
$AUC_{[0-72]}$	Mean (SD)	84.49 (48.615)	91.18 (55.451)	83.55 (41.368)
(ng·hr/mL)	CV (%)	57.54	60.81	49.51
	Min, Max	17.59, 166.99	26.20, 207.92	26.83, 166.17
C_{max}(ng/mL)	Mean (SD)	2.66 (1.728)	3.01 (2.017)	3.02 (1.846)
	CV (%)	64.88	66.93	61.22
	Min, Max	0.54, 5.49	0.70, 7.35	0.82, 6.40
T_{max}(hr)	Mean (SD)	23.43 (4.926)	25.71 (4.065)	23.71 (5.539)
	Median	24.00	24.00	24.00
	Min, Max	12.00, 28.00	20.00, 36.00	12.00, 36.00

Table: Summary of pharmacokinetic parameters for N-desethyloxybutynin by treatment regimen (adopted from the sponsor's study report table 11-3)

Parameter	Statistic	OTG Alone	Sunscreen/OTG	OTG/Sunscreen
$AUC_{[0-72]}$	Mean (SD)	73.13 (58.254)	80.88 (58.750)	69.55 (53.163)
(ng·hr/mL)	CV (%)	79.66	72.63	76.44
	Min, Max	19.05, 191.90	14.45, 182.64	10.88, 184.03
C_{max}(ng/mL)	Mean (SD)	2.17 (1.751)	2.31 (1.735)	2.18 (1.710)
	CV (%)	80.79	75.13	78.62
	Min, Max	0.53, 5.62	0.47, 5.16	0.38, 6.07
T_{max}(hr)	Mean (SD)	24.71 (5.744)	27.43 (1.453)	22.57 (8.993)
	Median	26.00	28.00	24.00
	Min, Max	6.00, 28.00	24.00, 28.00	2.00, 36.00

Table: DEO:OXY AUC0-72 ratios following OTG application by sunscreen treatment regimen (adopted from sponsor's study report table 11-4)

Statistic	OTG Alone	Sunscreen/OTG	OTG/Sunscreen
Mean (SD)	0.82 (0.252)	0.86 (0.275)	0.78 (0.270)
SEM	0.067	0.073	0.072
CV (%)	30.81	32.12	34.65
Min, Max	0.42, 1.25	0.33, 1.33	0.27, 1.20

Study OG06006

Title: A steady-state evaluation of the effect of showering on the absorption of oxybutynin following application of oxybutynin topical gel.

Objective: The primary objective of the study was to evaluate the effect of showering after application of OTG on the bioavailability of oxybutynin based on plasma concentrations of oxybutynin and N-desethyloxybutynin. The secondary objective was to assess safety based on the occurrence of adverse events.

Methods: The study was a multiple dose, four-period, open-label, randomized, crossover design evaluating the effect of showering on the bioavailability of oxybutynin from the topical gel. The study consisted of daily outpatient dosing of 1 gm of 10% OTG for 35 consecutive days: beginning with 13 days of outpatient OTG application, inpatient OTG application and inpatient showering on Day 14, and inpatient serial blood sampling for 24 hours on Days 14, 21, 28, and 35. On the pharmacokinetic sampling days, subjects were enrolled in one of four regimens: no shower, showering 1 hour post-dose, 2 hours post-dose, or 6 hours post-dose in a randomized sequence. A different showering regimen took place on Days 21, 28, and 35. Each subject participated in each showering or no showering regimen once during the study. OTG was applied by the subjects to rotating sites on the upper arms/shoulders, abdomen and thighs. There were 4 inpatient clinic visits that included confinement for approximately 36 hours for gel application, serial blood sampling and a 5 minute showering regimen. The water temperature for the showering was maintained at 110ºF and all subjects washed each leg, torso, and each arm for approximately 1 minute per area with Neutrogena® Liquid Cleansing Formula. There was a minimum of 7 days between each sampling period. Of the twenty subjects enrolled, fifteen (6 males and 9 females) completed the study. Most subjects were Caucasians. The mean (SD) age was 26.9 (6.90) years old with a range of 18 to 45.

Pharmacokinetic Sampling: Blood samples for plasma concentrations of OXY and DEO were taken within 30 minutes prior to the first inpatient dose in each period, and at approximately 1, 1.5, 2, 2.5, 3, 6.5, 7, 12, and 24 hours after dose. Of the twenty subjects enrolled, fifteen (6 males and 9 females) completed the study.

Results:
Based on the data presented on the effect of showering, the overall systemic exposure of OXY and its metabolism to DEO following OTG application was not significant. The biggest difference in the mean (SD) AUC_{0-24} (15.6% lower) was observed for the showering 2-hours post-dose group compared to the no shower group (113.5 (62.48) vs. 134.7 (84.99) ng.hr/mL); however, there was significant variability observed with all the individual subjects in both groups and this difference does not appear to be clinically relevant. With the exception of the 'Showering 2-hours post-dose" group with a C_{avg} of about 4 ng/mL, the C_{avg} for the other groups were about 6 ng/mL. The C_{avg} is expected to range from 4 to 6 ng/ml, according to the multiple dose study (OG04008).

Showering did appear to affect the T_{max} (time to reach maximum concentration) for oxybutynin Without showering the mean (SD) T_{max} was 12.30 (11.70) hours, which is similar to that observed in the multiple dose study (OG04008) of 13.14 (8.37) hours for OTG applied to the abdomen. With showering, the mean T_{max} was decreased to 3.13, 5.63, and 8.03 for the showering 1-hour, 2-hour, and 6-hour post-dose groups, respectively. The sponsor states that a shorter T_{max} is likely to have resulted from an increase in peripheral blood flow in response to the heat from the warm water during showering and increase in the skin temperature to facilitate an increase in transdermal absorption. This reviewer concurs with this rationale for the observed changes in T_{max}. It is noted that although the T_{max} shortened, the overall exposure as indicated by AUC_{0-24} was not significantly altered. It also appears that showering did not

alter the metabolism of OXY to DEO as observed by the DEO:OXY ratio of approximately 1 for all shower groups.
Each showering session was 5 minutes in duration with the water temperature at 110°F and hypoallergenic soap.

Subjects were randomized to one of 3 application sequences:
1. abdomen: thigh: upper arm/shoulder
2. upper arm/shoulder: abdomen: thigh
3. thigh: upper arm/shoulder: abdomen

Subjects were further randomized to one of four showering sequences:
1. No shower: 6 hours: 1 hour: 2 hours
2. 1 hour: no shower: 2 hours: 6 hours
3. 2 hours: 1 hour: 6 hours: no shower
4. 6 hours: 2 hours: no shower: 1 hour

Figure: Mean (SEM) plasma OXY and DEO concentration vs. time profile during the "No Shower" Regimen (adopted from the sponsor's study report figure 11-1)

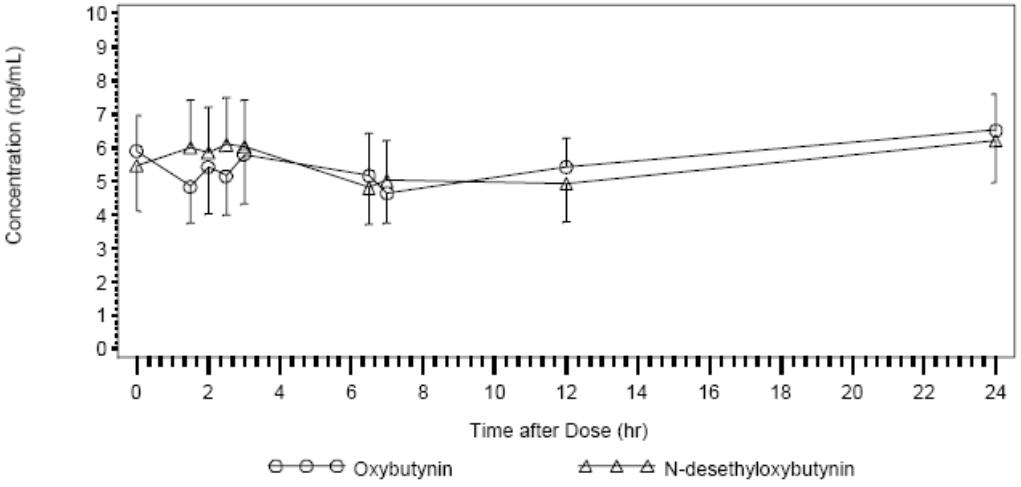


Figure: Mean (SEM) plasma OXY and DEO concentration vs. time profile during the "1-Hour Post-Dose" Showering Regimen (adopted from the sponsor's study report figure 11-2)

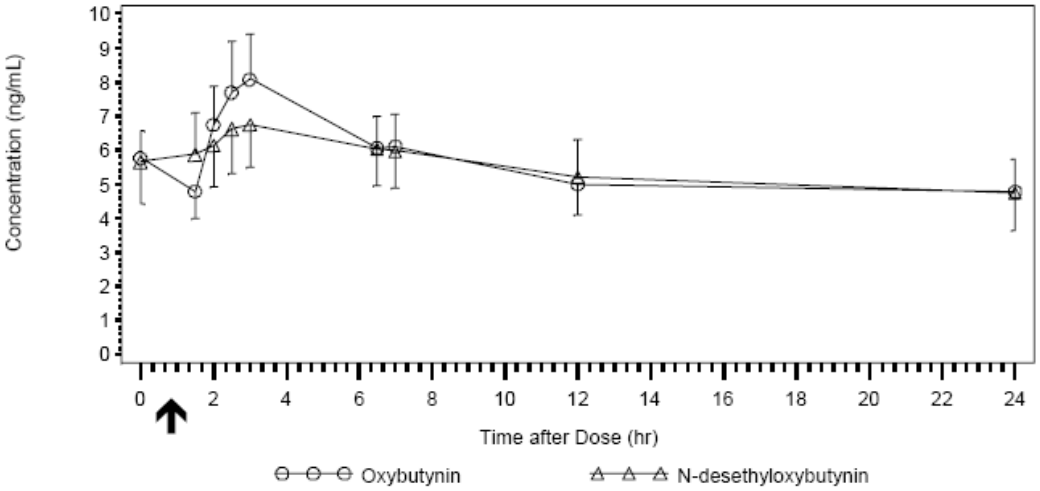


Figure: Mean (SEM) plasma OXY and DEO concentration vs. time profile during the "2-Hour Post-Dose" Showering Regimen (adopted from the sponsor's study report figure 11-3)

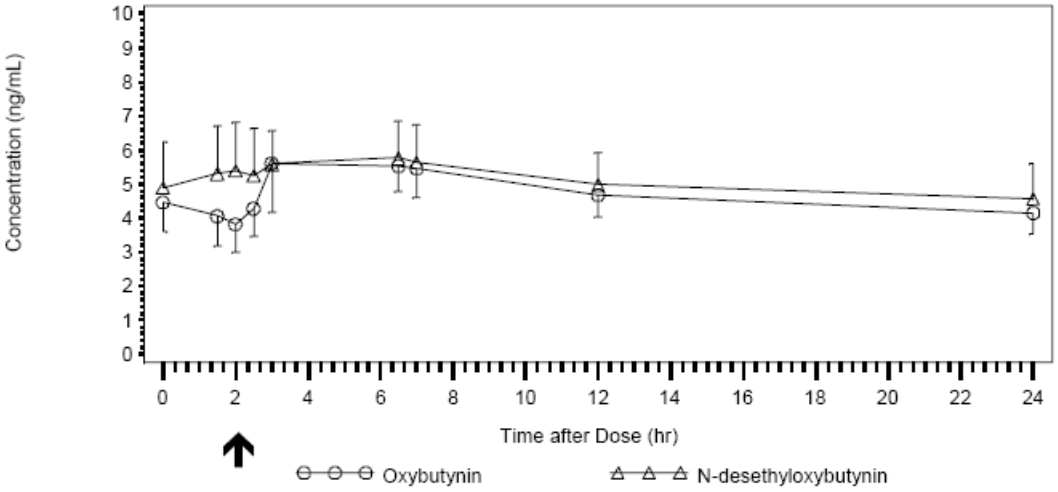


Figure: Mean (SEM) plasma OXY and DEO concentration vs. time profile during the "6-Hour Post-Dose" Showering Regimen (adopted from the sponsor's study report figure 11-4)

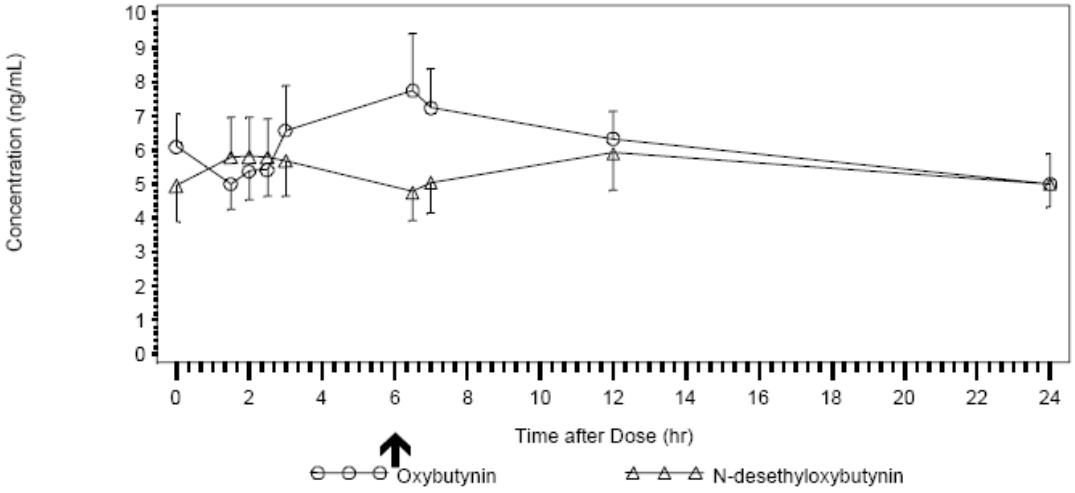


Figure: Mean (SEM) plasma OXY concentration vs. time profile for each showering regimen (adopted from the sponsor's study report figure 11-5)

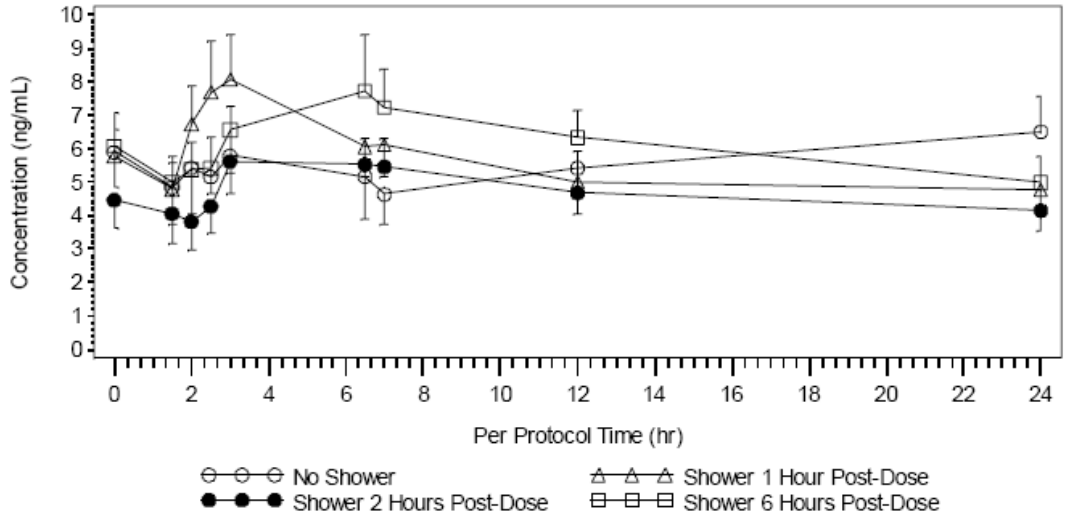


Table: Summary of OXY pharmacokinetic parameters by showering regimen (adopted from the sponsor's study report table 11-2)

Parameter	Statistic	Shower Regimen			
		No Shower	Shower 1 Hour Post Dose	Shower 2 Hours Post Dose	Shower 6 Hours Post Dose
$AUC_{[0-24]}$ (ng·hr/mL)	Mean (SD)	134.4 (84.99)	132.8 (84.74)	113.5 (62.48)	147.2 (69.62)
	SEM	21.94	21.88	16.13	17.98
	CV (%)	63.23	63.82	55.05	47.29
	Min, Max	30.18, 306.6	35.21, 310.9	29.55, 257.6	31.68, 270.5
C_{max} (ng/mL)	Mean (SD)	8.58 (5.74)	9.17 (6.43)	6.49 (3.30)	10.10 (6.49)
	SEM	1.48	1.66	0.85	1.68
	CV (%)	66.86	70.07	50.84	64.24
	Min, Max	1.49, 22.40	1.61, 23.70	1.69, 14.70	1.54, 22.10
T_{max} (hr)	Mean (SD)	12.30 (11.70)	3.13 (2.10)	5.63 (4.02)	8.03 (7.79)
	SEM	3.02	0.54	1.04	2.01
	Median	12.00	3.00	6.50	6.50
	Min, Max	0.00, 24.00	0.00, 7.00	0.00, 12.00	0.00, 24.00
DEO:OXY	Mean (SD)	0.93 (0.38)	0.98 (0.32)	1.00 (0.39)	0.92 (0.41)
	SEM	0.10	0.08	0.10	0.10
	CV (%)	41.33	32.19	39.22	44.04
	Min, Max	0.43, 1.79	0.44, 1.50	0.30, 1.87	0.29, 1.57

Study OG06007

Title: An evaluation of the person-to-person transference and absorption potential of oxybutynin following application of oxybutynin topical gel to healthy volunteers.

Objective: The primary objective of the study was to determine if topically applied oxybutynin could be transferred between treated and untreated subjects by direct physical contact with the application site of the treated subject. The secondary objective was to evaluate whether clothing could prevent drug transfer from one individual to another.

Methods: The study was a single dose, open-label, randomized, parallel group design. Subjects were randomized to receive either a single dose of 1 gm 10% OTG applied to the abdomen or no OTG treatment. Of those randomized to receive OTG, subjects were assigned to cover the application site with clothing or remain unclothed following application. The treated and untreated subjects engaged in direct physical contact/movement with the application site (abdomen-to-abdomen) for 15 minutes after 1 hour post dose for the treated subjects. The duration of treatment for each subject was 1 to 2 days. Fifty two subjects participated in the study with 26 in the Safety Population and 25 in the Evaluable Population. Forty-five subjects were Caucasian, two were African-American, one was biracial, and four were Hispanic. The mean (SD) age was 25.1 (5.48) with a range of 18 to 44 years.

Pharmacokinetic Sampling: Blood samples were taken for OXY and DEO from the untreated subjects at 0 hours (before contact) and at 2, 4, 8, 12, 24, 36, and 48 hours after contact with the application site. A single sample was drawn from treated subjects 3 hours following contact (4 hours post dose) as a control to verify dosing, but the data were not included in the study report.

Results

The data from this study demonstrated that transference of OXY and DEO from a treated subject to an untreated subject can occur through vigorous physical contact when the contact site is unprotected with clothing. The mean (SD) exposure (AUC_{0-48}) for OXY was 0.24 (0.62) and 29.78 (24.46) ng.hr/mL for all subjects covered with clothing and for all subjects with skin-to-skin contact with the treated subjects, respectively. Though transfer was observed in the skin-to-skin contact group, the mean (SD) C_{max} for OXY of 0.94 (0.75) ng/mL was substantially lower than observed single dose C_{max} of 4.53 ng/mL in Study OG04007. Of the subjects who were exposed to OXY while wearing clothing, none were male subjects. It appears that females from both groups are more susceptible to transference from contact with subject treated with OTG, possibly due to women having thinner skin compared to men.

For DEO, the mean (SD) AUC_{0-48} was 0.00 (0.00) and 33.26 (36.04) ng.hr/mL for all subjects covered with clothing and subjects with skin-to-skin contact with all treated subjects, respectively. The mean (SD) C_{max} was 0.00 (0.00) and 1.01 (1.05) ng/mL for all subjects covered with clothing and for all subjects with skin-to-skin contact with the treated subjects, respectively.

Overall, clothing appears to be an appropriate method to prevent transfer of OXY and DEO from a partner using OTG. The recommendation is that the application site should be covered with clothing once OTG has dried in order to prevent transfer of OXY and DEO to an untreated person.

Figure: Mean (SEM) plasma OXY vs. time profiles of all untreated subjects following skin-to-skin and clothing-to-skin contact with application sites of treated subjects (adopted from sponsor's study report figure 11-1)

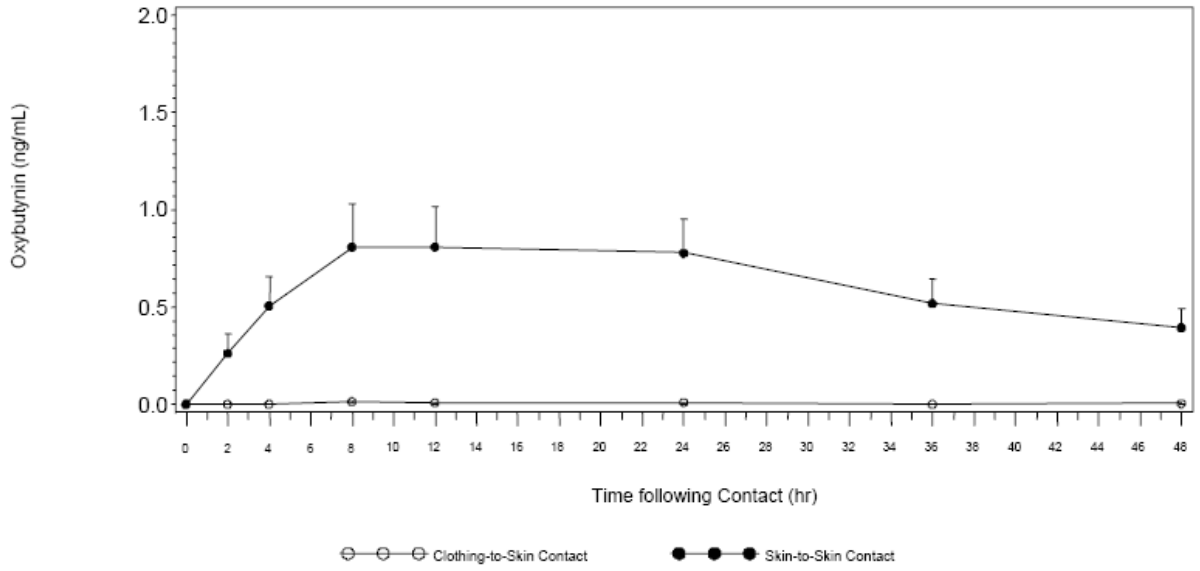


Table: Summary of pharmacokinetic parameters of OXY following skin-to-skin contact regimen (adopted from sponsor's study report table 11-2)

Parameter	Statistic	All Subjects (n = 12)	Female Subjects (n=7)	Male Subjects (n=5)
$AUC_{[0-48]}$ (ng·hr/mL)	Mean (SD)	29.78 (24.458)	37.67 (28.998)	18.73 (11.056)
	SEM	7.060	10.960	4.944
	CV (%)	82.13	76.98	59.02
	Min, Max	9.37, 85.66	10.96, 85.66	9.37, 32.53
C_{max} (ng/mL)	Mean (SD)	0.94 (0.747)	1.14 (0.879)	0.66 (0.450)
	SEM	0.216	0.332	0.201
	CV (%)	79.53	76.96	68.73
	Min, Max	0.30, 2.28	0.35, 2.28	0.30, 1.21
T_{max} (hr)	Mean (SD)	17.27 (7.459)	15.70 (8.142)	19.47 (6.573)
	SEM	2.153	3.077	2.939
	Median	18.27	12.27	24.27
	Min, Max	8.27, 24.27	8.27, 24.27	12.27, 24.27

Table: Summary of pharmacokinetic parameters of OXY following clothing-to-skin contact regimen (adopted from sponsor's study report table 11-3)

Parameter	Statistic	All Subjects (n = 14)	Female Subjects (n=8)	Male Subjects (n=6)
$AUC_{[0-48]}$ (ng·hr/mL)	Mean (SD)	0.24 (0.624)	0.43 (0.796)	0.00 (0.000)
	SEM	0.167	0.281	0.000
	CV (%)	255.23	186.03	--
	Min, Max	0.00, 1.86	0.00, 1.86	0.00, 0.00
C_{max} (ng/mL)	Mean (SD)	0.01 (0.032)	0.02 (0.041)	0.00 (0.000)
	SEM	0.008	0.014	0.000
	CV (%)	259.54	189.61	--
	Min, Max	0.00, 0.10	0.00, 0.10	0.00, 0.00
T_{max} (hr) *	Mean (SD)	8.27 (0.000)	8.27 (0.000)	--
	SEM	0.000	0.000	--
	Median	8.27	8.27	--
	Min, Max	8.27, 8.27	8.27, 8.27	--
	N	2	2	0

*Because some subjects had all BLQ concentrations, T_{max} was not applicable in those subjects and not included in the calculation of descriptive statistics.

Figure: Mean (SEM) plasma DEO vs. time profiles following skin-to-skin contact and clothing-to-skin contact for all untreated subjects (adopted from sponsor's study report figure 14.2.1-10)

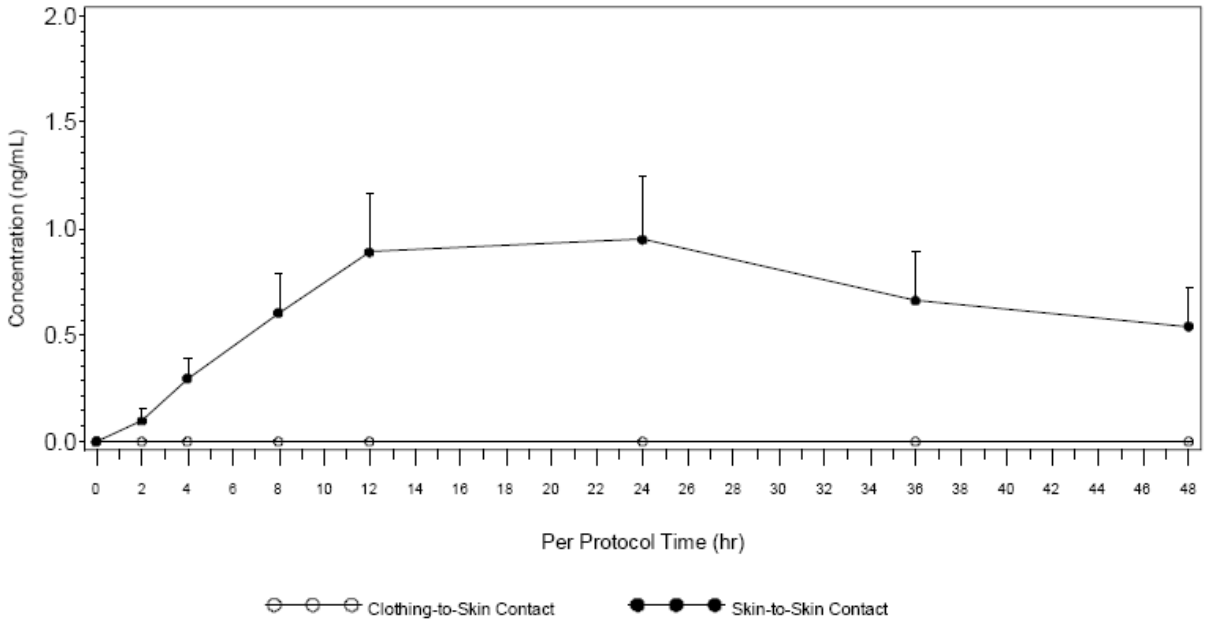


Table: Summary of pharmacokinetic parameters of DEO following clothing-to-skin contact and skin-to-skin contact regimens (adopted from sponsor's study report table 14.2.2-2)

		Contact Regimen	
Pharmacokinetic Parameter	Statistic	Clothing-to-Skin Contact N=14	Skin-to-Skin Contact N=12
AUC[0-48] (ng·hr/mL)	Mean (SD)	0.00 (0.000)	33.26 (36.036)
	SEM	0.000	10.403
	CV (%)	--	108.33
	Min, Max	0.00, 0.00	4.83, 110.46
	n	14	12
Cmax (ng/mL)	Mean (SD)	0.00 (0.000)	1.01 (1.052)
	SEM	0.000	0.304
	CV (%)	--	104.03
	Min, Max	0.00, 0.00	0.17, 3.07
	n	14	12
Tmax (hr)	Mean (SD)	--	19.27 (6.179)
	SEM	--	1.784
	Median	--	24.27
	Min, Max	--	12.27, 24.27
	n	0	12

Because some subjects had all BLQ concentrations, Tmax was not applicable and not included in the calculation of descriptive statistics.

Table: Summary of pharmacokinetic parameters of DEO following clothing-to-skin contact and skin-to-skin contact regimens for untreated female subjects (adopted from sponsor's study report table 14.2.2-4)

		Contact Regimen	
Pharmacokinetic Parameter	Statistic	Clothing-to-Skin Contact N=8	Skin-to-Skin Contact N=7
AUC[0-48] (ng·hr/mL)	Mean (SD)	0.00 (0.000)	47.10 (42.176)
	SEM	0.000	15.941
	CV (%)	--	89.54
	Min, Max	0.00, 0.00	12.53, 110.46
	n	8	7
Cmax (ng/mL)	Mean (SD)	0.00 (0.000)	1.41 (1.229)
	SEM	0.000	0.465
	CV (%)	--	86.99
	Min, Max	0.00, 0.00	0.38, 3.07
	n	8	7
Tmax (hr)	Mean (SD)	--	20.84 (5.855)
	SEM	--	2.213
	Median	--	24.27
	Min, Max	--	12.27, 24.27
	n	0	7

Because some subjects had all BLQ concentrations, Tmax was not applicable and not included in the calculation of descriptive statistics.

Table: Summary of pharmacokinetic parameters of DEO following clothing-to-skin contact and skin-to-skin contact regimens for untreated male subjects (adopted from sponsor's study report table 14.2.2-4)

		Contact Regimen	
Pharmacokinetic Parameter	Statistic	Clothing-to-Skin Contact N=6	Skin-to-Skin Contact N=5
AUC[0-48] (ng·hr/mL)	Mean (SD)	0.00 (0.000)	13.89 (9.935)
	SEM	0.000	4.443
	CV (%)	--	71.51
	Min, Max	0.00, 0.00	4.83, 29.90
	n	6	5
Cmax (ng/mL)	Mean (SD)	0.00 (0.000)	0.45 (0.314)
	SEM	0.000	0.140
	CV (%)	--	70.01
	Min, Max	0.00, 0.00	0.17, 0.91
	n	6	5
Tmax (hr)	Mean (SD)	--	17.07 (6.573)
	SEM	--	2.939
	Median	--	12.27
	Min, Max	--	12.27, 24.27
	n	0	5

Because some subjects had all BLQ concentrations, Tmax was not applicable and not included in the calculation of descriptive statistics.

Study OG05009

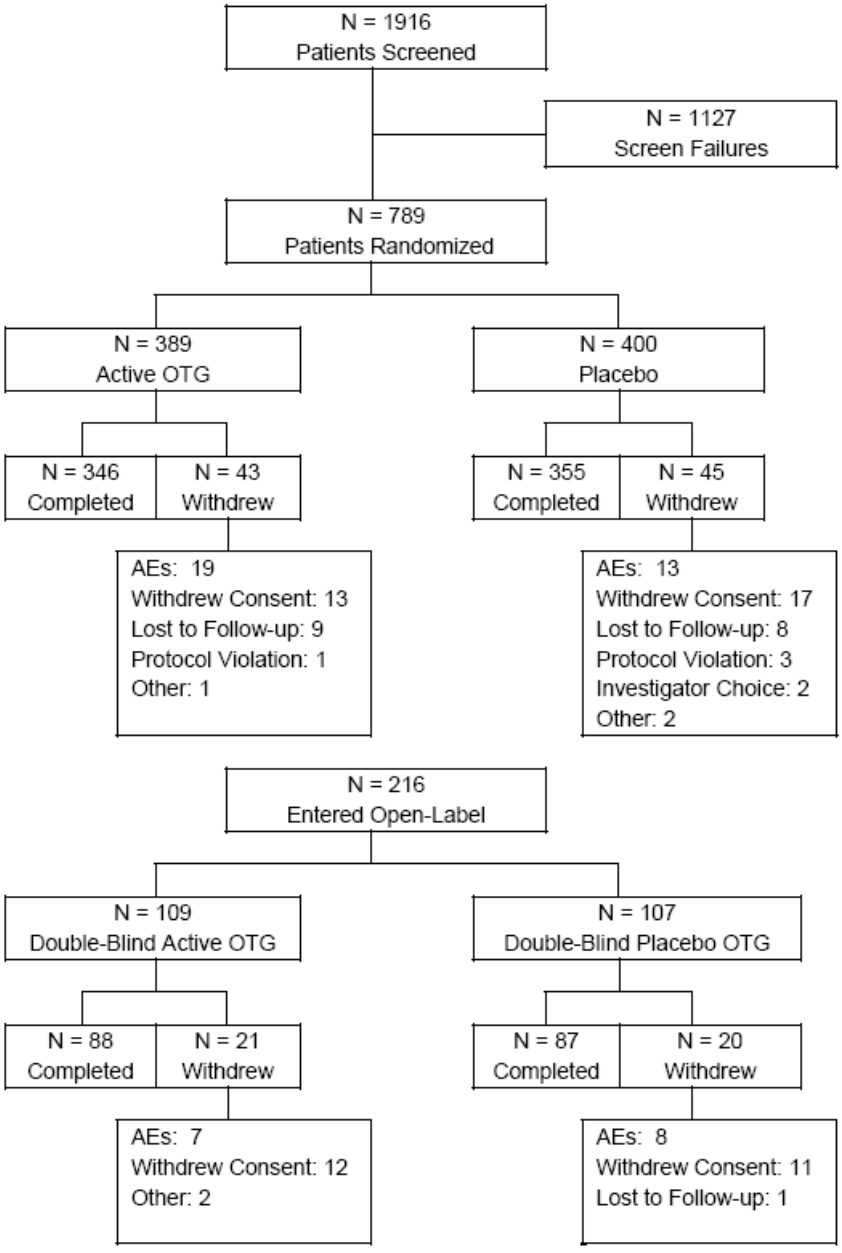
Title: A multi-center, double-blind, placebo-controlled study of the efficacy and safety daily dosing with Oxybutynin Topical Gel to treat the symtoms of Overactive Bladder with a 14-week open-label safety extension.

Objective: The primary objective of the Phase 3 study was to compare the efficacy of daily treatment of a 1 gm dose of 10% OTG with placebo gel treatment during a 12-week study period. The primary efficacy endpoint was the change from baseline to endpoint (Week 12 Last Observation Carried Forward [LOCF]) in the number of incontinence episodes per day recorded on a 3-day urinary dairy. The secondary objectives included comparing additional efficacy measures and safety assessments for OTG treatment versus placebo. In addition, the sponsor took blood samples to measure plasma concentrations of OXY and DEO to evaluate population PK of the product. The study included a 14-week open-label safety extension to demonstrate continued systemic and dermatologic safety of treatment with OTG in patients with OAB.

Methods: The study was a multi-center, randomized, double-blind, placebo-controlled, parallel group Phase 3 study followed by an open-label safety extension. The study consisted of three periods: (1) a screening period of 3 to 4 weeks, inclusion of a 2-week period for washout from current pharmacological treatment for OAB and practice of bladder and fluid management techniques at the first study visit, a 1-week baseline evaluation to complete the 3-day urinary dairy, and an additional 1-week period, if necessary, to repeat the 3-day urinary dairy; (2) a 12-week, randomized, double-blind, placebo-controlled treatment period; and (3) a 14-week, optional, open-label, treatment period. During the double-blind and open-label treatment periods, 1 gm of 10% OTG was applied to rotating sites on the abdomen, upper arms/shoulders, or thighs for 12 weeks and 14 weeks, respectively.

A the 1916 patients screened for participation, 789 patients were enrolled and randomized to 76 study sites: 400 received placebo and 389 received active OTG treatment. Seven hundred and one (88.8%) of the 789 randomized patients completed the double-blind period of the study. Of the 701 patients who completed the double-blind period, 216 entered into the open-label safety extension period from 24 selected study sites. One hundred seventy-five (81.0%) of the 216 patients who entered the open-label safety period completed the 14 additional weeks of treatments.

The following is a flow chart and table of patient disposition in the study.


N = 1916
Patients Screened
N = 1127
Screen Failures
N = 789
Patients Randomized
N = 389
Active OTG
N = 400
Placebo
N = 346
Completed
N = 43
Withdrew
N = 355
Completed
N = 45
Withdrew
AEs: 19
Withdrew Consent: 13
Lost to Follow-up: 9
Protocol Violation: 1
Other: 1
AEs: 13
Withdrew Consent: 17
Lost to Follow-up: 8
Protocol Violation: 3
Investigator Choice: 2
Other: 2
N = 216
Entered Open-Label
N = 109
Double-Blind Active OTG
N = 107
Double-Blind Placebo OTG
N = 88
Completed
N = 21
Withdrew
N = 87
Completed
N = 20
Withdrew
AEs: 7
Withdrew Consent: 12
Other: 2
AEs: 8
Withdrew Consent: 11
Lost to Follow-up: 1

Disposition	Placebo N= 400	OTG N= 389	Overall N= 789
Number of Patients n (%)			
Completed	355 (88.8%)	346 (88.9%)	701 (88.8%)
Discontinued	45 (11.3%)	43 (11.1%)	88 (11.2%)
Discontinuation Due To:			
Adverse Event	13 (3.3%)	19 (4.9%)	32 (4.1%)
Protocol Violation	3 (0.8%)	1 (0.3%)	4 (0.5%)
Refusal or Inability to Participate Further	17 (4.3%)	13 (3.3%)	30 (3.8%)
Lost to Follow-Up	8 (2.0%)	9 (2.3%)	17 (2.2%)
Investigator Recommendation	2 (0.5%)	0 (0.0%)	2 (0.3%)
Other	2 (0.5%)	1 (0.3%)	3 (0.4%)

Pharmacokinetic Sampling: Blood samples were collected for measurement of OXY and DEO concentrations only during the 12-week double-blind treatment period. Upon completion at Weeks 1, 4, 8, and 12 when the patients were required to visit the clinic, blood samples were taken for measurement of OXY and DEO.

Results:

The mean plasma concentrations for OXY and DEO were consistent across all study visits. The mean (SD) for OXY and DEO concentrations at endpoint were 5.98 (5.87) and 7.10 (8.05) ng/mL, respectively for active treated patients.

Table 11-16: Summary of Plasma Oxybutynin and N-Desethyloxybutynin Concentrations (ng/mL) by Double-Blind Period Visit for Active OTG Patients (mITT population)

Visit	Statistic	OXY	DEO	Ratio
Visit 4 (Week 1)	Mean	6.2714	6.7622	1.1330
	SD	5.5932	6.3264	0.4848
	n	364	364	358
Visit 5 (Week 4)	Mean	6.0655	6.6682	1.1642
	SD	5.2420	6.4556	0.6222
	n	357	357	354
Visit 6 (Week 8)	Mean	6.0519	6.7993	1.1844
	SD	5.3808	7.0633	0.6988
	n	338	340	329
Visit 7 (Week 12)	Mean	6.1097	7.1712	1.2194
	SD	5.8980	7.8167	0.9534
	n	308	308	296

Source: Table 14.4-1, Listing 16.2.5-2

Linear regression was used to assess whether there was a relationship between the change from baseline in efficacy parameters for urinary incontinence episodes, average daily urinary frequency, and urine volume per void and plasma concentrations; age and plasmsa concentrations; weight and plasma

concentrations; and BMI and plasma concentrations for each visit. No meaningful correlation was found between higher plasma OXY or DEO concentrations and improved efficacy or increased side effects.

Figure 14.4-9: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by Visit (mITT Population)
Part 1: Visit 4 (OC)

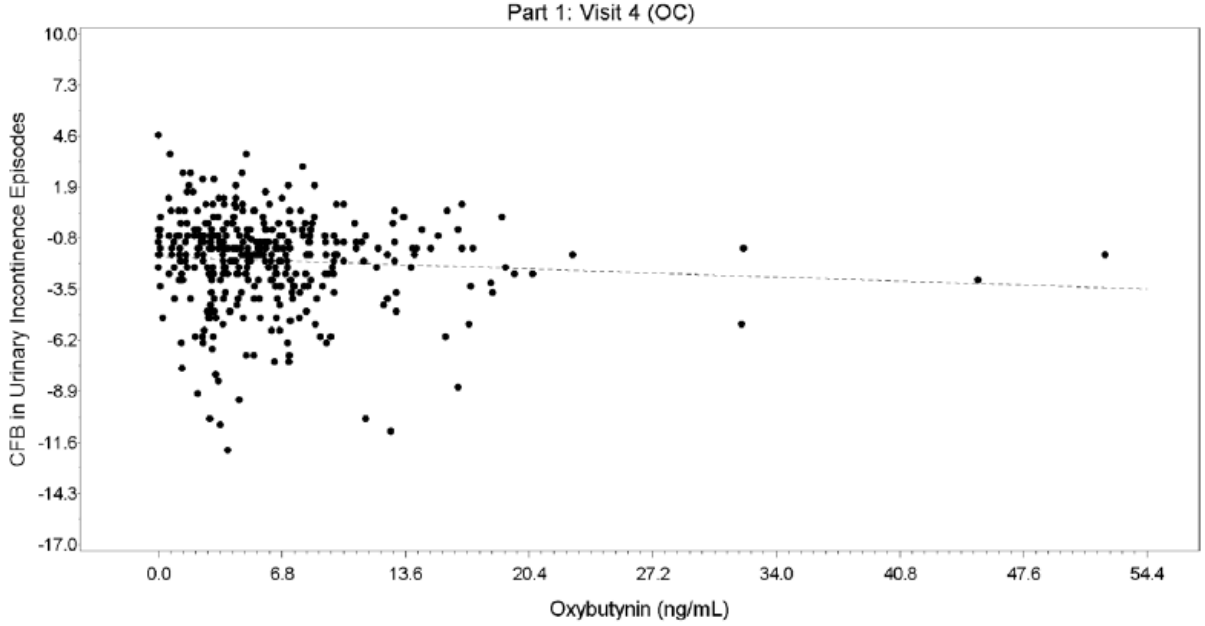


Figure 14.4-9: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by Visit (mITT Population)
Part 2: Visit 5 (OC)

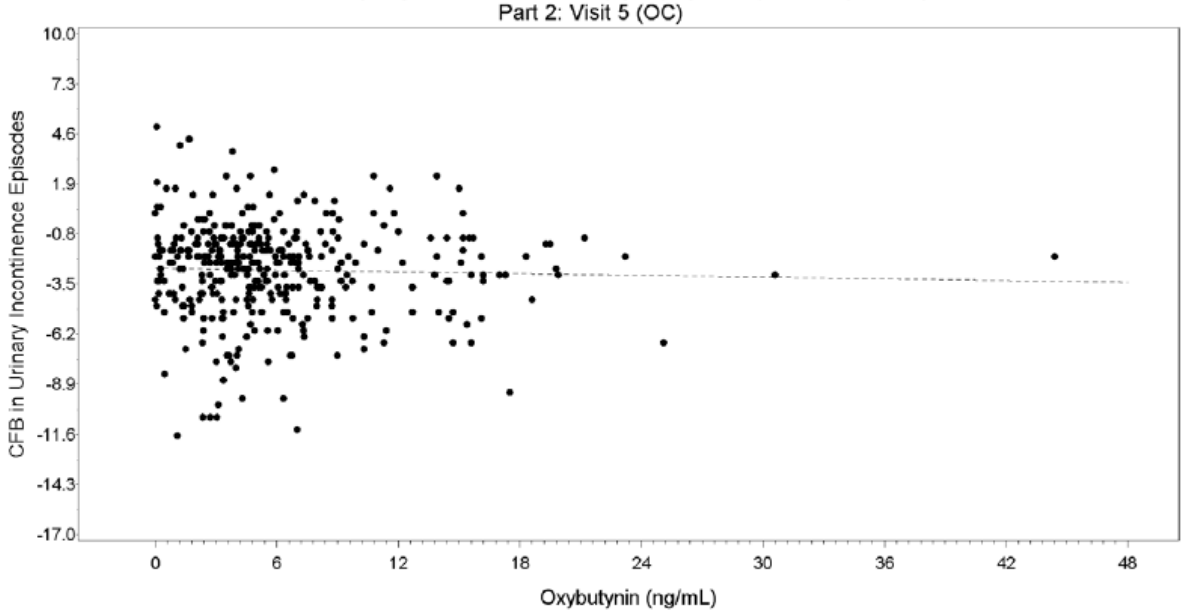


Figure 14.4-9: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by Visit (mITT Population)
Part 3: Visit 6 (OC)

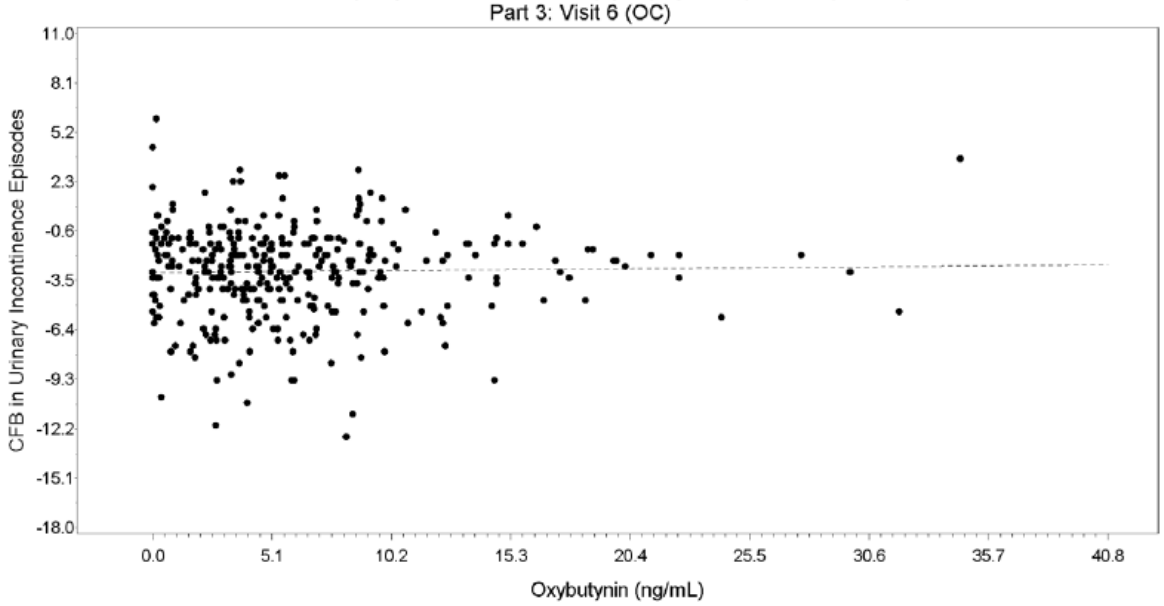


Figure 14.4-9: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by Visit (mITT Population)
Part 4: Visit 7 (OC)

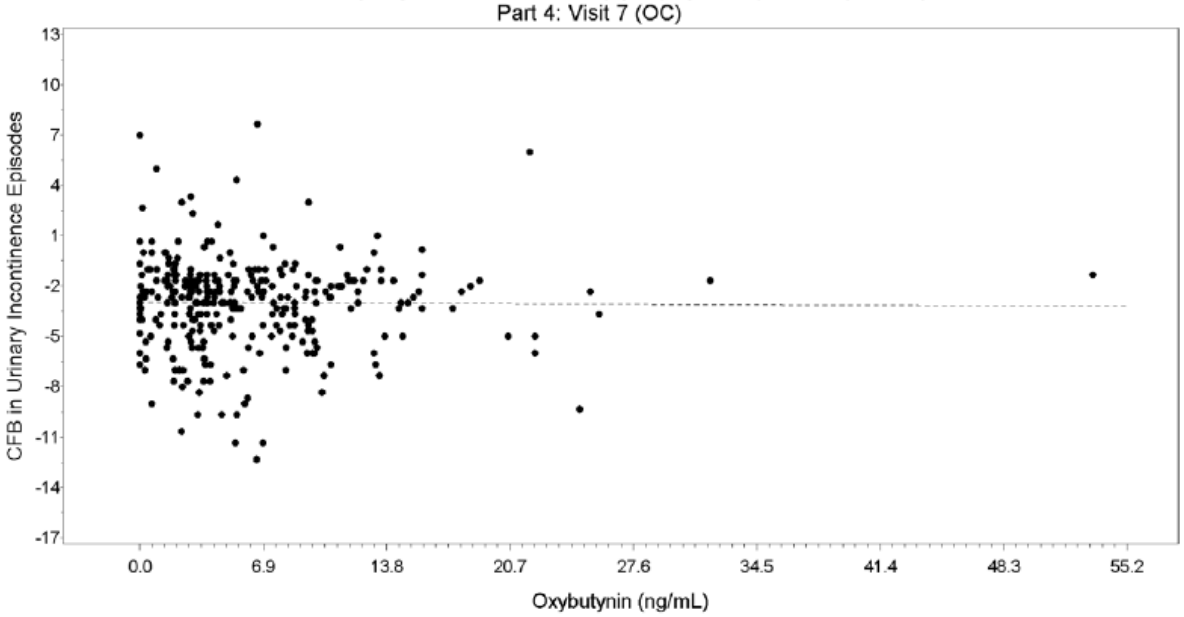


Figure 14.4-9: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by Visit (mITT Population)
Part 5: Endpoint (LOCF)

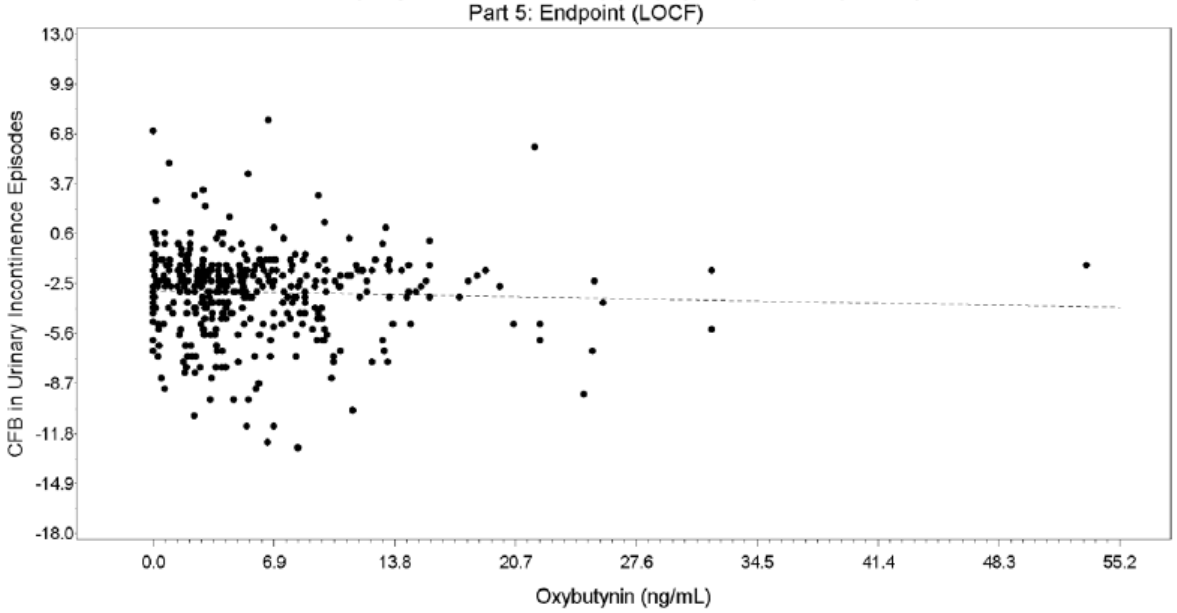


Figure 14.4-10: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by BMI Category
Part 1: BMI < 32 kg/m2

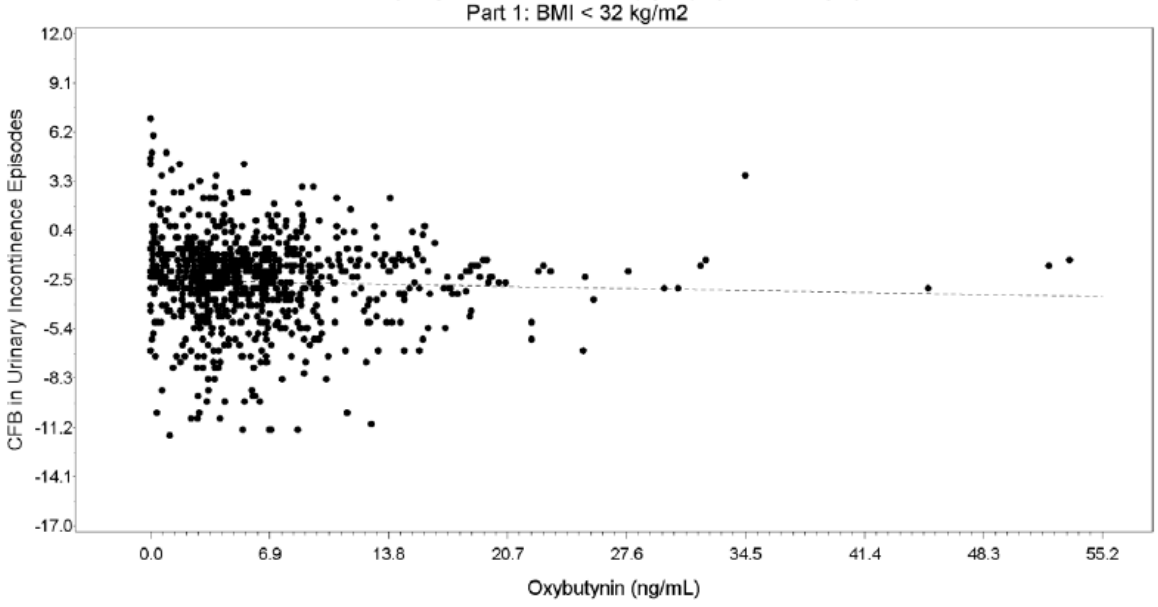


Figure 14.4-11: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by Geriatric Status
Part 1: Age < 65 years

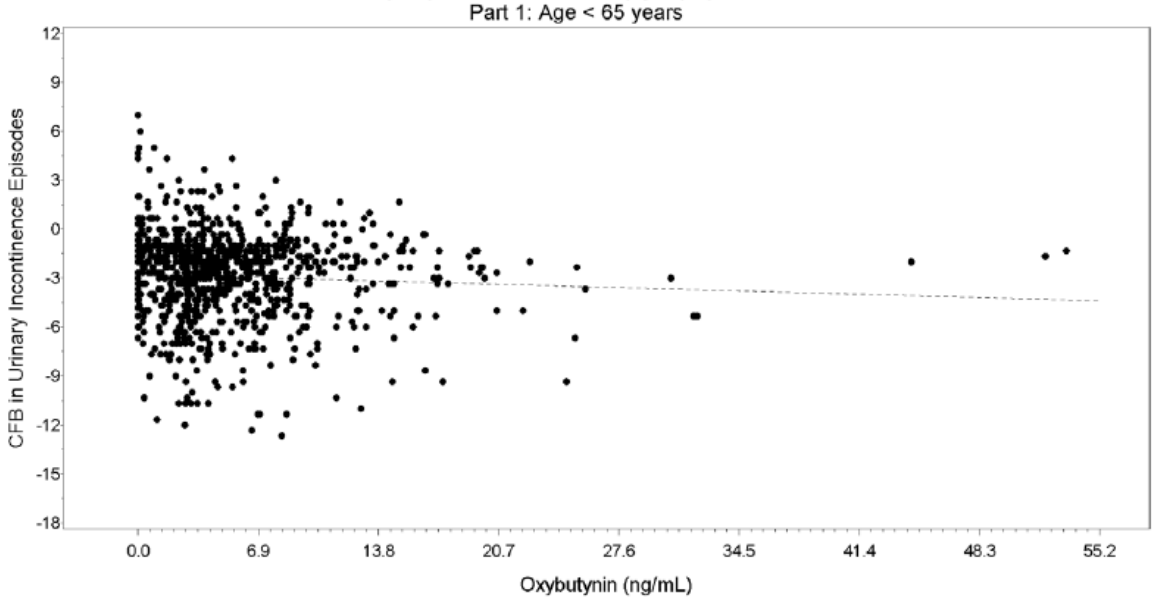
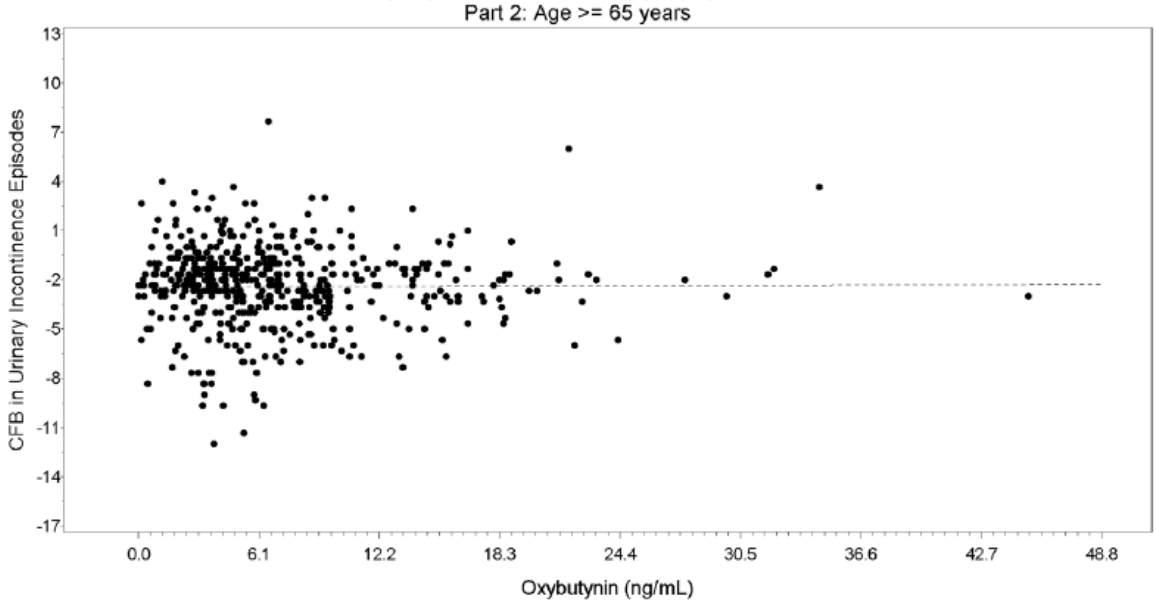


Figure 14.4-11: Regression Plots for Change From Baseline in Urinary Incontinence Episodes and Plasma Oxybutynin Concentrations (ng/ml) by Geriatric Status
Part 2: Age >= 65 years



Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-204**	**Brand Name**	
OCP Division	**DCP3**	**Generic Name**	**Oxybutynin Chloride**
Medical Division	**DRUP**	**Drug Class**	
OCP Reviewer	**LaiMing Lee, Ph.D.**	**Indication(s)**	**Treatment of Overactive Bladder**
OCP Team Leader	**Myong-Jin Kim, Pharm.D.**	**Dosage Form**	**Topical Gel**
		Dosing Regimen	**1 gm daily**
Date of Submission	**3/27/08**	**Route of Administration**	**topical**
Estimated Due Date of OCP Review		**Sponsor**	**Watson Laboratories**
PDUFA Due Date	**1/27/09**	**Priority Classification**	**S**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**	**2**	**Study OG03005** **Study OG04007**
multiple dose:	**X**	**1**	**1**	**Study OG04008**
Patients-				
single dose:				
multiple dose:	**X**	**1**	**1**	**Study OG05009**

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability –	**X**	**5**	**0**	**Study OG02020 - Pilot BA Study OG03013 – BA at different surface areas Studies OG03018 & OG04004 – Comparative BA of initial formulations Study OG04008 - BA of oxybutynin at different application sites**
solution as reference:				
alternate formulation as reference:	**X**	**1**	**1**	**Study OG06005 – Bioavailability of Oxybutynin Topical Gel and Oxytrol® patch**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				

III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Extrinsic Factors	**X**	**3**	**3**	**Study OG06001 - Use with sunscreen** **Study OG06006 - Effect of Showering** **Study OG06007 - Person-to-Person Transfer**
Total Number of Studies		**12**	**8**	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**What are the mulitple dose parameters? (What is the relative bioavialability of oxybutynin topical gel and the approved oxybutynin transdermal patch?)** **What extrinsic factors influence dose-exposure and/or response and what is the impact of any differences in exposure on response?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology Review

NDA: 22-204

Compound: Oxybutynin Chloride 10% Topical Gel

Sponsor: Watson Laboratories

Date: 05/30/08

Reviewer: LaiMing Lee, Ph.D.

Background: Oxybutynin chloride is an anticholinergic agent used for the treatment of Overactive Bladder (OAB) Syndrome. It is an antimuscarinic agent that has been previously approved as an immediate release (IR) oral tablet (Ditropan®), extended release (ER) oral tablet (Ditropan XL®), oral syrup (Ditropan®), and ER transdermal patch (Oxytrol®). The sponsor claims that 1 gram of 10% Oxybutynin Topical Gel (OTG) administered daily was effective in the treatment of OAB as measured by: significant reductions in the number of daily incontinence episodes, daily urinary frequency, and increase in volume per void. Additionally, the sponsor states the most frequently reported treatment-related adverse events in patients receiving OTG were dry mouth (6.9%) and application site reaction (2.1%); however, treatment with OTG was associated with a lower incidence of both anticholinergic and application site adverse events.

Development history: Watson currently markets Oxytrol® and has designed the topical gel to have similar pharmacokinetic characteristics to those of the transdermal patch. The sponsor states that an unoccluded gel system was considered to be potentially more convenient to use and should produce less skin irritation compared to the patch. Optimization of the active drug substance concentration was achieved with in vitro skin permeation studies using gels with oxybutynin chloride concentrations of 22 mg/g (2.2%), 44 mg/g (4.4%), 66 mg/g (6.6%), 88 mg/g (8.8%) and 132 mg/g (13.2%). The greatest increase in flux occurred between 2.2% and 4.4% while concentrations greater than 4.4% showed no significant effect on oxybutynin skin flux.

Watson also conducted a pilot in vitro bioavailability study using human cadaver skin and concluded that an average of 2.9% of the applied dose is absorbed across the skin over 24 hours. Based on this finding it was estimated that 3.36 g (4.2 mL) of a 4.4 % gel would be required to deliver an equivalent amount of oxybutynin (3.9 mg/day) to achieve equivalent systemic concentrations of oxybutynin as the Oxytrol® transdermal patch. To reduce the application volume, Watson later reformulated the product that resulted in a (b) (4) and a 1 g sachet of 10% oxybutynin.

Formulation History of Oxybutynin Topical Gel:

Sachet Code #	Date Introduced	Oxybutynin Chloride Content (mg/g)	Sachet Fill (g)	Reason for Formulation Change
		(b) (4)		

Bioavailability: Watson conducted eleven Phase 1 bioavailability/pharmacokinetic studies to evaluate the pharmacokinetics and metabolism of OTG in single and multiple dose applications, as well as effects from showering, sunscreen, and skin contact transference. The absolute bioavailability of oxybutynin is about 6% for both the IR tablet and syrup. The sponsor did not perform absolute bioavailability studies with OTG; however, it was previously determined that the 39 cm^2 Oxytrol® transdermal patch has a nominal in vivo delivery rate of 3.9 mg oxybutynin per day. Study OG04007 was a comparative bioavailability/pharmacokinetic study comparing the 3.9 mg/day Oxytrol® to 3 g of 4.4% OTG, 1 g of 10% OTG, and 3 g of 10% OTG. The results from this study showed that each of these formulations produced measurable and potentially therapeutic concentrations of oxybutynin in comparison to Oxytrol®. On a dose-normalized basis, 1 g of 10% OTG produced the most comparable AUC_{0-144} to the transdermal patch.

Absorption: Oxybutynin is rapidly absorbed following administration of the IR oral tablet with a C_{max} within one hour and an effective half life of approximately 2 to 3 hours. Steady state oxybutynin plasma concentrations are achieved by Day 3 of repeated dosing of the ER oral tablets. For the topical gel, steady state concentrations are reached within 7 days of continuous dosing. A multiple dose, steady state pharmacokinetic study was conducted (Study OG06005) in healthy subjects to evaluate the relative bioavailability of 1 g of 10% OTG and Oxytrol®.

Distribution: The volume of distribution of oxybutynin is 193 L after intravenous administration of 5 mg oxybutynin chloride. The plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration.

Metabolism: Oxybutynin (OXY) is metabolized primarily by cytochrome P450s, particularly CYP3A4 found mostly in the liver and gut wall. The metabolites of oxybutynin include phenylcyclohexylglycolic acid, which does not possess pharmacological activity, and desethyloxybutynin (DEO), which is pharmacologically active. The plasma concentration of DEO is 5 times higher than OXY with the ER formulations and 10 to 20 times higher for the IR formulations. After reaching steady state, OXY and DEO demonstrated biphasic elimination with plasma concentrations beginning to decrease 24 hours after dosing. There was rapid elimination between 24 and 48 hours after dosing followed by a more prolonged terminal elimination phase. The apparent elimination half-lives were 64 hours and 82 hours for OXY and DEO, respectively.

Excretion: Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted as unchanged OXY in the urine. Less than 0.1% of the administered dose is excreted as the metabolite DEO.

Special population: For Oxytrol®, gender, age, and weight did not appear to significantly affect the pharmacokinetics of OXY and DEO following application. The sponsor stated that one objective of the Phase 3 clinical study (OG05009) was to evaluate the population pharmacokinetics of OTG. Plasma concentrations of OXY and DEO were measured with comparisons in pharmacokinetic parameters made between (1) men and women; (2) young and elderly; and (3) caucasian and non-caucasian.

Clinical vs. to-be-marketed formulation: (b) (4) The sponsor conducted a comparative bioavailability study (Study OG04007) using 39 cm Oxytrol®, 3 g of 4.4% OTG, 1 g of 10% OTG, and 3 g of 10% OTG. Per sponsor, each of these formulations produced measurable and potentially therapeutic concentrations of oxybutynin in comparison to Oxytrol®. On a dose-normalized basis, 1 g of 10% OTG produced the most comparable AUC_{0-144} to the transdermal patch.

The Phase 3 clinical efficacy and safety study (Study OG05009) was conducted using 1 g sachet of the 10% OTG (Sachet Code # 0599). The to-be-marketed product has the same composition as the product used in the pivotal Phase 3 study.

Composition of the to-be-marketed 10% OTG, 100 mg/g (1.14 mL)

Component	% by Weight	mg/g	Function
Oxybutynin chloride, USP	10.0	100	Drug Substance
Purified Water, USP		(b) (4)	
Alcohol, USP			
Glycerin, USP			
Sodium Hydroxide, (Sodium Hydroxide, NF and Purified Water, USP)			
Hydroxypropyl Cellulose, NF			

Single Dose Pharmacokinetic Studies: The sponsor conducted several single dose PK studies as part of their development and exploratory activities to optimize the formulation before conducting the Phase 3 study.

Single Dose Comparative Pharmacokinetics Study: The sponsor conducted a single dose PK study to compare new higher concentration gel formulations with the original 4.4% OTG and TDS. This Phase 1 study (OG04007) was a single dose, four-period, open-label, randomized, crossover study comparing the PK of 39 cm^2 TDS, 3 g of 4.4% OTG, 1 g of 10% OTG, and 3 g of 10% OTG. The abdomen was the application site for all treatments and began 7 days

following the previous treatment. Blood samples (10 mL) were drawn within 30 minutes prior to the first dose in each period, and at approximately 2, 6, 12, 16, 20, 24, 32, 36, 44, 48, 52, 56, 72, 84, 96, 120, and 144 hours after each dose. Twenty of the twenty-two subjects completed all four treatment periods of the study.

Table 11-6 Summary of Dose-Normalized Oxybutynin + N-desethyloxybutynin $AUC_{[0-144]}$ by Treatment.

Parameter	Statistic	39 cm² TDS	3g 4.4% gel	1g 10% gel	3g 10% gel
Dose-Normalized AUC[0-144] (ng·hr/mL)	Mean (SD)	175.54 (65.77)	325.02 (110.92)	219.46 (78.51)	498.92 (212.43)
	SEM	14.71	24.80	17.56	47.50
	CV (%)	37.47	34.13	35.78	42.58
	Min, Max	89.23, 313.88	206.69, 612.36	118.16, 414.90	240.61, 1178.35
	n	20	20	20	20

Source: Table 14.2.2-3, Listings 16.2.6-1, 2

Using nonlinear regression software program, the sponsor used single dose plasma concentration data to model a single compartment, first-order absorption and elimination PK model. The modeled plasma concentration profile for each individual was used for determination of PK parameters, which were then used as input variables into a PK simulation program to predict plasma concentration profiles for 14 days of daily dosing OTG and every 84 hours for Oxytrol®. The simulations suggest that daily dosing of 1 g 10% OTG will provide comparable steady state plasma concentration profiles to every 3.5 days of 39 cm^2 Oxytrol®. The steady state model was tested in a multiple dose steady state study (OG06005).

Multiple Dose Pharmacokinetic Study: The sponsor evaluated multiple dose PK study of OXY and DEO following 1 g of 10% OTG. The Phase 1 study (OG06005) was a two-period, open-label, randomized crossover design of multiple applications of OTG and TDS to evaluate the comparative steady-state plasma concentrations of PK of each product. Twenty-two healthy male and female subjects were enrolled (20 subjects completed the study) and randomized to receive 18 daily doses of OTG or 5 consecutive TDS (4 x 3.5 days, followed by one 4-day application). There was a minimum 14-day washout period between the two treatments and the application site was rotated on the abdomen, thighs, and upper arms/shoulder. In each dosing period, blood samples were collected for analysis of R and S enantiomers of OXY and DEO during the final 4 days of dosing (Days 15-18). Blood samples (10 mL) were drawn within 30 minutes prior to the first inpatient dose in each period, and at approximately 12, 24, 36, 48, 60, 72, 84, and 96 hours post-dose.

Table 11-2 **Summary of Oxybutynin Pharmacokinetic Parameters for OTG and TDS Applications (Evaluable Population)**

Parameter	Statistic	OTG N = 20	TDS N = 20
$AUC_{[0-96]}$ (ng·hr/mL)	Mean (SD)	321.7 (112.3)	312.5 (67.62)
	SEM	25.12	15.12
	CV (%)	34.92	21.64
	Min, Max	146.8, 578.5	191.5, 430.0
C_{avg} (ng/mL)	Mean (SD)	3.35 (1.17)	3.26 (0.70)
	SEM	0.26	0.16
	CV (%)	34.92	21.64
	Min, Max	1.53, 6.03	1.99, 4.48
C_{max} (ng/mL)	Mean (SD)	5.99 (2.58)	4.82 (1.31)
	SEM	0.58	0.29
	CV (%)	43.13	27.15
	Min, Max	2.30, 10.20	2.35, 8.16
C_{min} (ng/mL)	Mean (SD)	1.78 (0.60)	1.77 (0.58)
	SEM	0.13	0.13
	CV (%)	33.54	32.48
	Min, Max	0.80, 3.65	0.74, 3.11
T_{max} (hr)	Mean (SD)	36.00 (33.04)	40.80 (23.49)
	SEM	7.39	5.25
	Median	30.00	36.00
	Min, Max	0.00, 96.00	12.00, 72.00

Source: Table 14.2.1-1 Part 1, Listing 16.2.6-1

Multiple Dose Pharmacokinetic and Application Site Bioavailability Study: In a Phase 1 study (Study OG04008), the sponsor evaluated the in vivo steady state pharmacokinetics of OXY and its enantiomers following multiple dose applications of 1 g of 10% OTG and evaluated the relative bioavailability of OXY when applied to various areas of the body. Forty healthy male and female subjects were enrolled in a multiple dose, randomized, crossover study to compare the steady state pharmacokinetics of the formulation at different application sites (abdomen, upper arm/shoulder, and thigh). The treatment period was 42 days in duration at which time the subjects applied daily 1 g of 10% OTG each morning, had three 36-hour inpatient visits for serial blood sampling on Days 14-15, 28-29, and 42-43, and six outpatient visits for single daily blood samples following the final OTG application. Blood samples were assayed for the R and S enantiomers of OXY and DEO. Blood samples (10 mL) for PK analysis were collected from a forearm vein and were drawn within 30 min prior to the first dose in each period, and at approximately 2, 4, 6, 8, 12, 16, 20, and 24 hours after the dose. Single morning blood samples were drawn daily following the final gel application through study day 49.

Table 11-2 Summary of Pharmacokinetic Parameters for Oxybutynin following Gel Applications to the Abdomen, Thigh and Upper Arm/Shoulder (N=39).

Parameter	Statistic	Abdomen	Thigh	Upper Arm/Shoulder
$AUC_{[0-24]}$	Mean (SD)	112.69 (57.997)	125.12 (84.674)	133.78 (81.578)
(ng·hr/mL)	CV (%)	51.47	67.67	60.98
	Min, Max	16.11, 268.90	22.16, 395.11	16.40, 373.45
C_{max}(ng/mL)	Mean (SD)	6.77 (3.933)	6.97 (4.949)	8.26 (5.972)
	CV (%)	58.09	71.00	72.26
	Min, Max	0.94, 21.70	1.71, 25.00	1.00, 31.50
C_{avg} (ng/mL)	Mean (SD)	4.66 (2.395)	5.18 (3.503)	5.54 (3.375)
	CV (%)	51.39	67.64	60.94
	Min, Max	0.67, 10.98	0.90, 16.21	0.68, 15.24
C_{min}(ng/mL)	Mean (SD)	3.27 (2.157)	3.84 (2.829)	3.49 (2.352)
	CV (%)	65.98	73.62	67.35
	Min, Max	0.00, 9.96	0.15, 13.72	0.05, 12.00
T_{max}(hr)	Mean (SD)	13.14 (8.370)	13.53 (9.075)	13.53 (8.210)
	Median	16.00	16.00	16.00
	Min, Max	-0.50, 24.00	-0.50, 24.00	-0.50, 24.00

Source: Table 14.2.2-1, Listing 16.2.6-1

Table 11-3 Summary of Pharmacokinetic Parameters for DEO following Gel Applications to the Abdomen, Thigh and Upper Arm/Shoulder (N=39).

Parameter	Statistic	Abdomen	Thigh	Upper Arm/Shoulder
$AUC_{[0-24]}$	Mean (SD)	109.31 (87.385)	118.81 (104.604)	114.10 (75.770)
(ng·hr/mL)	CV (%)	79.94	88.04	66.41
	Min, Max	9.85, 518.65	21.07, 644.22	15.97, 374.78
C_{max}(ng/mL)	Mean (SD)	5.44 (3.969)	6.12 (5.109)	6.07 (4.102)
	CV (%)	72.92	83.55	67.59
	Min, Max	0.68, 22.85	1.14, 31.50	0.81, 19.45
C_{avg} (ng/mL)	Mean (SD)	4.52 (3.588)	4.92 (4.351)	4.73 (3.148)
	CV (%)	79.41	88.44	66.60
	Min, Max	0.41, 21.17	0.88, 26.84	0.67, 15.62
C_{min}(ng/mL)	Mean (SD)	3.67 (3.310)	4.07 (3.865)	3.68 (2.417)
	CV (%)	90.08	95.03	65.60
	Min, Max	0.00, 19.08	0.12, 23.60	0.41, 11.63
T_{max}(hr)	Mean (SD)	14.18 (9.909)	14.51 (9.881)	14.72 (9.974)
	Median	16.00	20.00	24.00
	Min, Max	-0.50, 24.00	2.00, 24.00	0.00, 24.00

Source: Table 14.2.2-2, Listing 16.2.6-2

Table 11-5: Application Site Bioequivalence for Oxybutynin and DEO

Variable	Comparison (Test:Reference)	PK Parameter	Ratio	90% Confidence Interval	Bioequivalence Achieved?
Oxybutynin	Thigh: Abdomen	$AUC_{[0-24]}$	1.07	0.93,1.23	YES
		C_{max}	0.99	0.85,1.16	YES
	Arm:Abdomen	$AUC_{[0-24]}$	1.14	0.99,1.31	NO
		C_{max}	1.14	0.97,1.33	NO
DEO	Thigh: Abdomen	$AUC_{[0-24]}$	1.09	0.95,1.26	NO
		C_{max}	1.11	0.96,1.28	NO
	Arm:Abdomen	$AUC_{[0-24]}$	1.09	0.94,1.25	NO
		C_{max}	1.13	0.98,1.30	NO

Source: Tables 14.2.3-1and 2, Appendix 16.1.9.2

The sponsor states that the statistical analyses of the AUC and Cmax parameters comparing application sites showed OXY absorption at all three sites to be similar, but only strictly bioequivalent between the thigh and abdominal sites based on the 90% confidence intervals for OXY. DEO concentrations were not bioequivalent between thigh and abdominal sites, or for the upper arm/shoulder and abdomen for either PK parameters. The sponsor also states that PK parameters for the R and S enantiomers were similar between applications sites. Plasma concentrations of S-OXY (AUC0-24) were approximately 20% higher than R OXY concentrations, and conversely, R-DEO concentrations were apprximately 25% higher than S-DEO concentrations. The sponsor also states that the results from this study confirm the comparability of 1 g of 10% OTG and the 39 cm^2 TDS.

Phase 3 Clinical/Population Pharmacokinetics Study: Study OG05009 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study followed by an open-label safety extension. The study consisted of three periods: a 3 to 4-week screening period, a 12-week treatment period, and an optional 14-week open-label safety extension treatment period. The primary objective of the 12-week treatment period was to compare the safety and efficacy of daily treatment of 1 g of 10% OTG with placebo gel treatment. The primary endpoint for this part of the Phase 3 study was to evaluate the change from baseline to endpoint in the number of incontinence episodes per day recorded on a 3-day urinary diary. The secondary objectives included comparing additional efficacy measures and safety assessments for OTG treatment versus placebo. All patients applied 1 g of 10% OTG to rotating sites on the abdomen, upper arms/shoulders, or thighs. Patients were instructed to return to the clinic with their 3-day urinary diaries following 1, 4, 8, and 12 weeks of treatment to complete quality of life (QOL) questionaires, to have skin tolerability evaluations, to have blood samples drawn for pharmacokinetics evaluations, and for monitoring adverse events.

A 14-week open-label extension period was added onto the 12-week Phase 3 safety and efficacy study in order to obtain 6 months of safety data for at least 50 patients. During the extension period, patients were also instructed to apply daily a 1 g dose of 10% OTG to rotating sites on the abdomen, upper arms, shoulders, or thighs. Patients returned to the clinic following the additional 7 and 14 weeks of treatment for monitoring of vital signs, skin tolerability and adverse events. At the last extension study visit, fasting blood and urine samples were collected for clinical lab analysis.

As part of the secondary objectives of this study, the sponsor measured plasma concentrations of OXY and DEO to evaluate the population PK. For the following subgroups, the sponsor concludes:
Race: There are no clinically meaningful differences in pharmacokinetics of OXY based on race in healthy volunteers or patients.
Geriatric: There are no clinically meaningful differences in pharmacokinetics of OXY based on geriatric status in patients. There were 243 patients under 65 years old and 137 patients over or equal to 65 years old who completed OTG treatment.
Gender: There are no clinically meaningful differences in the pharmacokinetics of OXY based on gender in healthy volunteers or patients.

Sunscreen: The effect of sunscreen on the pharmacokinetics of oxybutynin was studied using a three-period, open-label, randomized crossover design of single applications of 1 g of 10% OTG (Study OG06001). Fourteen healthy male and female subjects completed (16 enrolled) all three treatment periods (OTG alone, OTG application preceded by sunscreen application, and OTG application followed by sunscreen application). The total duration of participation for each subject was approximately 46 days with a minimum 14 day washout period between each treatment period. Each subject received 3 applications of 1 gm of 10% OTG for abdomen application. Each subject also received 800 mg of Coppertone® Oil-Free Sunblock SPF 15 for application with OTG for the other 2 dosing days. Sunscreen application was completed 30 minutes before or 30 minutes after OTG application, based on the treatment sequence. Blood samples (10 mL) for PK analysis were collected from a forearm vein and were drawn within 30 min prior to the first dose in each period, and at approximately 2, 6, 12, 16, 20, 24, 28, 36, 48, and 72 hours after the dose.

Table 11-2 Summary of Pharmacokinetic Parameters for Oxybutynin by Treatment Regimen (N=14).

Parameter	Statistic	OTG Alone	Sunscreen/OTG	OTG/Sunscreen
$AUC_{[0-72]}$	Mean (SD)	84.49 (48.615)	91.18 (55.451)	83.55 (41.368)
(ng·hr/mL)	CV (%)	57.54	60.81	49.51
	Min, Max	17.59, 166.99	26.20, 207.92	26.83, 166.17
C_{max}(ng/mL)	Mean (SD)	2.66 (1.728)	3.01 (2.017)	3.02 (1.846)
	CV (%)	64.88	66.93	61.22
	Min, Max	0.54, 5.49	0.70, 7.35	0.82, 6.40
T_{max}(hr)	Mean (SD)	23.43 (4.926)	25.71 (4.065)	23.71 (5.539)
	Median	24.00	24.00	24.00
	Min, Max	12.00, 28.00	20.00, 36.00	12.00, 36.00

Source: Table 14.2.2-1, Listing 16.2.6-1

Table 11-3 Summary of Pharmacokinetic Parameters for DEO by Treatment Regimen (N=14).

Parameter	Statistic	OTG Alone	Sunscreen/OTG	OTG/Sunscreen
$AUC_{[0-72]}$	Mean (SD)	73.13 (58.254)	80.88 (58.750)	69.55 (53.163)
(ng·hr/mL)	CV (%)	79.66	72.63	76.44
	Min, Max	19.05, 191.90	14.45, 182.64	10.88, 184.03
C_{max}(ng/mL)	Mean (SD)	2.17 (1.751)	2.31 (1.735)	2.18 (1.710)
	CV (%)	80.79	75.13	78.62
	Min, Max	0.53, 5.62	0.47, 5.16	0.38, 6.07
T_{max}(hr)	Mean (SD)	24.71 (5.744)	27.43 (1.453)	22.57 (8.993)
	Median	26.00	28.00	24.00
	Min, Max	6.00, 28.00	24.00, 28.00	2.00, 36.00

Source: Table 14.2.2-2, Listing 16.2.6-1

Based on their findings, the sponsor states that concomitant application of sunscreen, either before or after OTG application, had little effect on PK of OXY and DEO. The sponsor also states that the minor differences in AUC observed between regimens from the three conditions would not translate into a clinically meaningful difference in OXY concentrations.

Showering: The effect of showering at various times after application of 1 g of 10% OTG on the bioavailability, pharmacokinetics, and metabolism of oxybutynin was studied in a multiple-dose, open-label, randomized 4-way crossover design (Study OG06006). Fifteen subjects completed the study (20 subjects enrolled) and were instructed to apply the gel on the designated site and wash hands thoroughly after application. The study design consist of daily outpatient dosing with 1 gm of 10% OTG for 35 consecutive days and included inpatient serial blood sampling for 24 hours on Days 14, 21, 28, and 35. Blood samples were drawn within 30 minutes prior to the first inpatient dose in each period, and at approximately 1, 1.5, 2, 2.5, 3, 6.5, 7, 12 and 24 hours after the dose for analysis of OXYand DEO plasma concentrations. Each subject received 35 daily applications of OTG applied to rotating sites on the abdomen, upper arm/shoulder, and thighs. Each showering session was 5 minutes in duration with the water temperature at 110°F and hypoallergenic soap.

Subjects were randomized to one of 3 application sequences:

1. abdomen: thigh: upper arm/shoulder
2. upper arm/shoulder: abdomen: thigh
3. thigh: upper arm/shoulder: abdomen

Subjects were further randomized to one of four showering sequences:

1. No shower: 6 hours: 1 hour: 2 hours
2. 1 hour: no shower: 2 hours: 6 hours
3. 2 hours: 1 hour: 6 hours: no shower
4. 6 hours: 2 hours: no shower: 1 hour

Table 11-2 Summary of Oxybutynin Pharmacokinetic Parameters by Showering Regimen (N = 15). *Source: Tables14.2.2-1,7 Listings 16.2.6-1,2*

Parameter	Statistic	Shower Regimen			
		No Shower	Shower 1 Hour Post Dose	Shower 2 Hours Post Dose	Shower 6 Hours Post Dose
$AUC_{[0-24]}$ (ng·hr/mL)	Mean (SD)	134.4 (84.99)	132.8 (84.74)	113.5 (62.48)	147.2 (69.62)
	SEM	21.94	21.88	16.13	17.98
	CV (%)	63.23	63.82	55.05	47.29
	Min, Max	30.18, 306.6	35.21, 310.9	29.55, 257.6	31.68, 270.5
C_{max} (ng/mL)	Mean (SD)	8.58 (5.74)	9.17 (6.43)	6.49 (3.30)	10.10 (6.49)
	SEM	1.48	1.66	0.85	1.68
	CV (%)	66.86	70.07	50.84	64.24
	Min, Max	1.49, 22.40	1.61, 23.70	1.69, 14.70	1.54, 22.10
T_{max} (hr)	Mean (SD)	12.30 (11.70)	3.13 (2.10)	5.63 (4.02)	8.03 (7.79)
	SEM	3.02	0.54	1.04	2.01
	Median	12.00	3.00	6.50	6.50
	Min, Max	0.00, 24.00	0.00, 7.00	0.00, 12.00	0.00, 24.00
DEO:OXY	Mean (SD)	0.93 (0.38)	0.98 (0.32)	1.00 (0.39)	0.92 (0.41)
	SEM	0.10	0.08	0.10	0.10
	CV (%)	41.33	32.19	39.22	44.04
	Min, Max	0.43, 1.79	0.44, 1.50	0.30, 1.87	0.29, 1.57

The sponsor states that showering does not affect the overall systemic exposure of OXY and its metabolism following OTG application. Showering after application does appear to alter the t_{max},

bringing it closer to the time of showering, presumably due to a transient increase in peripheral blood flow in response to the heat from the shower.

The sponsor states in the label (section 12.3) that showering after 1 hour does not affect the overall systemic exposure to oxybutynin, but makes no recommendation on when a patient can shower following application of oxybutynin topical gel. Compared to no shower, the exposure (AUC_{0-24}) after 2 hours declined ~ 20 ng.hr/mL and after 6 hours increased ~ 10 ng.hr/mL. During the review process, a determination will be made on how the shower results can be used to guide patients on how to use the product if they intend to shower, bath, or swim after application.

Person-to-Person Transference: The potential for transfer of oxybutynin remaining on the skin after OTG application to an untreated person was evaluated in a single dose, open-label, randomized, parallel group design (Study OG06007). Fifty-two healthy male and female subjects were randomized to receive 1 gm of 10% OTG or no OTG. Those who received OTG treatment (14 males and 13 females) were further randomized to cover the application site or to remain unclothed following the application. Two scenarios were evaluated: one in which the treated and untreated subjects engaged in 15 minutes of sustained and direct skin-to-skin contact between the abdomen of the treated subject and the abdomen of the untreated subject; and another in which the treated subject wore clothing covering the application site during 15 minutes of sustained contact with the abdomen of the untreated subject (11 males and 14 females). Subjects were engaged in the direct physical contact 1 hour post-dose. Blood samples (10 mL) were taken from untreated subjects at 0 (before contact), 2, 4, 8, 12, 24, 36, and 48 hours after contact for assay of plasma concentrations of OXY and DEO. A single blood sample was taken from the treated subjects 3 hours following contact.

Table 11-2: Summary of Pharmacokinetic Parameters of Oxybutynin following Skin-to-Skin Contact Regimen (Safety Population).

Parameter	Statistic	All Subjects (n = 12)	Female Subjects (n=7)	Male Subjects (n=5)
$AUC_{[0-48]}$ (ng·hr/mL)	Mean (SD)	29.78 (24.458)	37.67 (28.998)	18.73 (11.056)
	SEM	7.060	10.960	4.944
	CV (%)	82.13	76.98	59.02
	Min, Max	9.37, 85.66	10.96, 85.66	9.37, 32.53
C_{max} (ng/mL)	Mean (SD)	0.94 (0.747)	1.14 (0.879)	0.66 (0.450)
	SEM	0.216	0.332	0.201
	CV (%)	79.53	76.96	68.73
	Min, Max	0.30, 2.28	0.35, 2.28	0.30, 1.21
T_{max} (hr)	Mean (SD)	17.27 (7.459)	15.70 (8.142)	19.47 (6.573)
	SEM	2.153	3.077	2.939
	Median	18.27	12.27	24.27
	Min, Max	8.27, 24.27	8.27, 24.27	12.27, 24.27

Source: Tables 14.2.2-1, 14.2.2-3, 14.2.2-5; Listings 16.2.6-1

Table 11-3: Summary of Pharmacokinetic Parameters of Oxybutynin following Clothing-to-Skin Contact Regimen (Safety Population).

Parameter	Statistic	All Subjects (n = 14)	Female Subjects (n=8)	Male Subjects (n=6)
$AUC_{[0-48]}$ (ng·hr/mL)	Mean (SD)	0.24 (0.624)	0.43 (0.796)	0.00 (0.000)
	SEM	0.167	0.281	0.000
	CV (%)	255.23	186.03	--
	Min, Max	0.00, 1.86	0.00, 1.86	0.00, 0.00
C_{max} (ng/mL)	Mean (SD)	0.01 (0.032)	0.02 (0.041)	0.00 (0.000)
	SEM	0.008	0.014	0.000
	CV (%)	259.54	189.61	--
	Min, Max	0.00, 0.10	0.00, 0.10	0.00, 0.00
T_{max} (hr) *	Mean (SD)	8.27 (0.000)	8.27 (0.000)	--
	SEM	0.000	0.000	--
	Median	8.27	8.27	--
	Min, Max	8.27, 8.27	8.27, 8.27	--
	N	2	2	0

*Because some subjects had all BLQ concentrations, T_{max} was not applicable in those subjects and not included in the calculation of descriptive statistics.

Source: Tables 14.2.2-1, 14.2.2-3, 14.2.2-5; Listings 16.2.6-1

The sponsor states that drug transfer and absorption occurred in all 12 untreated subjects following vigorous and sustained skin-to-skin contact; whereas clothing minimized and, in most cases (12 of 14), completely inhibited the absorption of oxybutynin in untreated subjects. The sponsor also states that drug transfer occurred in both male and female subjects; however female subjects generally absorbed more drug and attained higher mean maximum plasma oxybutynin concentrations than males.

Pharmacokinetics of Oxybutynin in Men versus Women: In the draft label under '***Gender***', the sponsor states (b) (4) The sponsor concluded that no clinically meaningful differences in PK (C_{ave} and C_{max}) in healthy men and women volunteers were observed based on the outcome of six separate clinical pharmacology studies (OG03005, OG03013, OG04008, OG06001, OG06005, and OG06006). The number of volunteers in these Phase 1 studies was limited with 16 to 40 subjects per study and a total of 140 enrolled. The sponsor also concluded that there was no clinically meaningful difference in the plasma concentrations of OXY and DEO by gender. Unlike the Phase 1 studies where the distribution of men and women in each study was nearly equal, the ratio of men to women in the Phase 3 study was approximately 1:10 (35 men and 345 women). With the limited number of subjects in the Phase 1 studies and heavily imbalanced distribution of men and women in the Phase 3 study, the sponsor does not adequately support their label claim that there is no clinically meaningful difference in PK based on gender.

Recommendation:

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 3 finds the Human Pharmacokinetics and Bioavailability section for NDA 22-204 acceptable for filing.

Review Issues/Comments:
During the review process the following areas will be of special interest to the Office of Clinical Pharmacology: Person-to-Person Transference; Use of Sunscreen; Showering; Race; Geriatric; and Gender.

With regard to the Person-to-Person Transference Study (OG06007), the sponsor states that a single blood sample from treated subjects were taken 3 hours following contact with the untreated subjects as a control to verify dosing; it appears that the data were not provided in the study report and will be requested from the sponsor.

_____ _____
LaiMing Lee, Ph.D., Primary Reviewer Date

_____ _____
Myong-Jin Kim, Pharm.D., Team Leader Date

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