CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-228 S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA	21,228/20,771
Submission Date	October 10, 2003
Brand Name	Detrol and Detrol LA
Generic Name	Tolterodine tartrate
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Pfizer
Submission Type; Code	Pediatric Exclusivity Submission; 3S
Dosing regimen	Daily or BID

Executive Summary

NDAs 21,228 and 20,771 are currently approved for urge urinary incontinence in adults at doses of 1 and 2 mg immediate release (IR) and 2 and 4 mg modified release (MR). Pfizer was issued a written request to conduct pediatric studies using tolterodine, dated January 23, 2001. The sponsor conducted 2 pharmacokinetic (PK)/safety studies, 3 pharmacokinetic/pharmacodynamic (PK/PD) studies and 2 phase 3 safety and efficacy trials. Additionally, since a non-marketed liquid was used in the younger children, 2 bioequivalence (BE) studies were also performed. The following table summarizes the submitted studies.

Study #	Study/Analysis Type	Design	Age	Dose/Dosage Form
018	PK and Safety Study	Open label, non-controlled, multiple dose, dose escalation	11-15 years	2 and 4 mg QD, prolonged release (MR) capsules
044	PK and Safety Study	Open label, non-controlled, multiple dose, dose escalation	5-10 years	0.5, 1, and 2mg BID immediate release (IR) tablet
001	Phase 1/2 PK/PD Study	Open label, non-controlled, multiple dose, dose escalation	1 month – 4 years	0.030, 0.060 and 0.120 mg/kg/day (BID), IR liquid preparation
002	Phase 1/2 PK/PD Study	Open label, non-controlled, multiple dose, dose escalation	5-10 years	0.030, 0.060 and 0.120 mg/kg/day (BID), IR liquid preparation
003	Phase 1/2 PK/PD Study	Open label, non-controlled, multiple dose, dose escalation	11-15 years	2 and 4 mg QD, MR capsules
008	Phase 3 Efficacy and Safety	Randomized, double blind, multicenter	5-10 years	2 mg QD, MR capsules
020	Phase 3 Efficacy and Safety	Randomized, double blind, multicenter	5-10 years (higher baseline micturitions than Study 008)	2 mg QD, MR capsules
018 and 044	Population-PK Analysis	Pooled population analysis of data from studies 018 and 044	5-15	See Study 018 and 044 descriptions above
018, 044, 008 and 020	Population-PK Analysis	Using the previously developed model, analysis of sparse sampling data from studies 008 and 020	5-15	See Study 018, 044, 008 and 020 descriptions above
004	Relative Bioavailability Study	open, randomized, 3-way, single-dose, crossover, PK study	Adults	2 different liquid IR solutions and tolterodine IR tablets
005	Relative Bioavailability Study	open, randomized, 2-way, single-dose, crossover, PK study	Adults	Opened MR capsules over applesauce and intact MR capsules

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the information included in the sNDA and has found that the

pharmacokinetics of tolterodine in children was adequately characterized; however, tolterodine use was not shown to be effective in the pediatric population.

Summary of Clinical Pharmacology/Biopharmaceutics Findings

Metabolism

Tolterodine is metabolized by CYP2D6 to active metabolite DD01 in extensive CYP2D6 metabolizers (EM) and metabolized by CYP3A4 to assorted inactive metabolites in poor CYP2D6 metabolizers (PM). Both tolterodine and DD01 have equal binding affinities to muscarinic receptors and lead to equal muscarinic receptor antagonism. As such, the sponsor defines the active moiety as the sum of the unbound tolterodine and DD01.

Pharmacokinetics

Two PK/safety trials were submitted for review. Study 044 (N=30, 28 EM, 2 PM) studied the safety and PK 0.5, 1, 2 and 3mg BID for 14 days of a non-marketed IR liquid preparation in 5-10 year olds. Study 018 (N=29, 27 EM, 2 PM) studied the safety and PK of 2 and 4mg QD for 6-10 days of the MR (Detrol LA) formulation.

Study 044 showed linear active moiety exposures over the dose range studied. According to the achieved exposures, 1 mg BID (IR liquid) in 5-10 year old children yields active moiety exposures similar to that achieved with standard 2 mg BID (IR tablets) dosing in adults. Distinction between the non-marketed IR liquid and IR tablets is made because the two preparations did not meet bioequivalence criteria (Study 004).

Study 018 also showed linear active moiety exposures over the dose range studied. In 11-15 year old children, 4 mg QD of the MR formulation yielded active moiety exposures similar to that achieved with the same dose/formulation in adults. However, these results were confounded by the fact that some children in the study, those with trouble swallowing the capsule, emptied the contents of the capsule over applesauce and ingested it instead of taking the capsule intact. Although the sponsor assumed these administration routes were bioequivalent, they in fact did not meet bioequivalence criteria in Study 005, a study conducted in adults to test the bioequivalence of intact and opened MR capsules.

Most adverse events noted are those consistent with muscarinic antagonism.

PK/PD

Three PK/PD studies were submitted for review. Studies 001, 002 and 003 were open label, non-controlled, multiple-dose, dose escalation studies in children with neurogenic disease. Studies 001 and 002 studied dose-response, using the non-marketed IR liquid, in children 3 month to 4 years of age and 5 to 10 years of age, respectively. Study 003 studied dose-response in 11 to 15 year old children using the MR formulation.

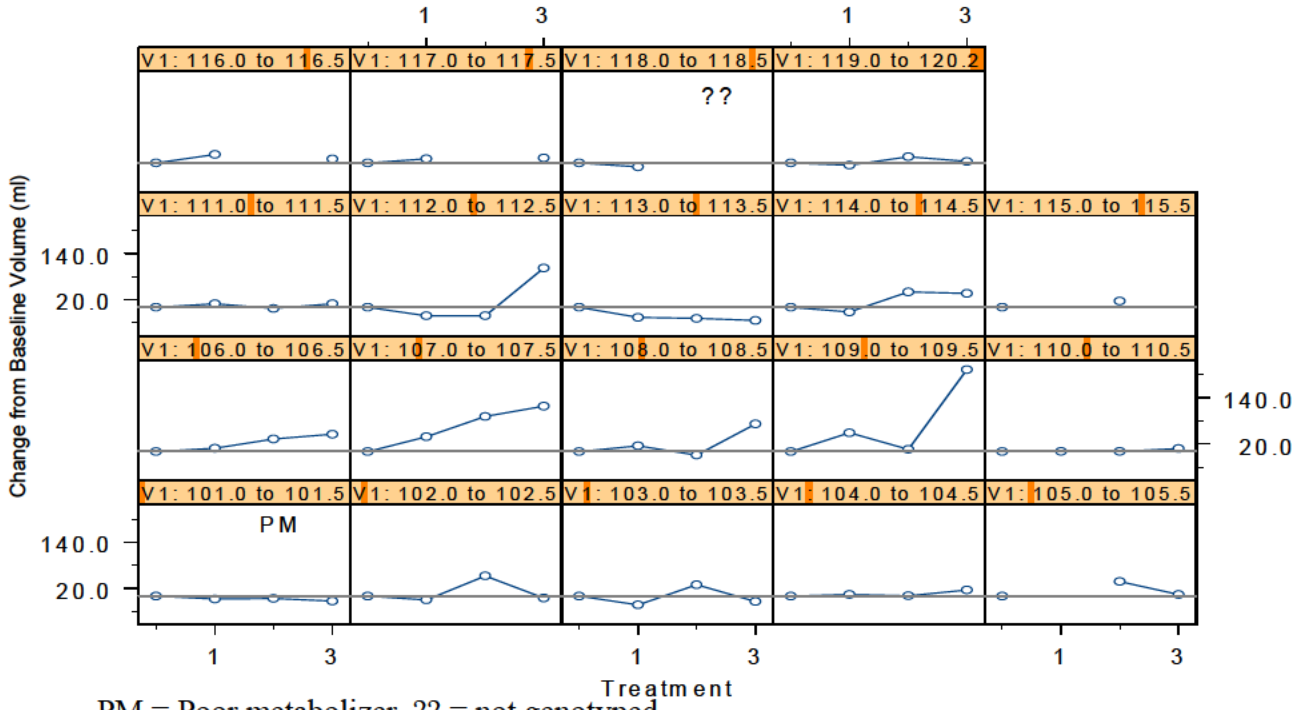
In all three studies, analysis of mean data suggested some dose-response relationship in several of the urodynamic variables that were measured, as seen below (Study 001).

Urodynamic Data; Study 001 (N=19)

Dose Period	Statistic	Volume to first detrusor contraction of magnitude >10 cm H_2O pressure (mL)	Functional bladder capacity (mL)	Leak point pressure (cm H_2O)
Baseline	Mean (SD)	21.7 (16.6)	74.2 (41.5)	49.0 (21.3)
	Median (min-max)	15.0 (4.0 to 60.0)	62.0 (13.0 to 160.0)	48.0 (12.0 to 90.0)
	Not reported	0	0	0
Period 1: 0.030 mg/kg/day	Mean (SD)	25.5 (22.9)	70.7 (33.5)	50.5 (29.3)
	Median (min-max)	22.0 (3.0 to 71.0)	73.0 (15.0 to 136.0)	47.0 (10.0 to 113.0)
	Not reported	2	0	1
Period 2: 0.060 mg/kg/day	Mean (SD)	38.9 (29.7)	101.6 (67.5)	40.9 (21.4)
	Median (min-max)	31.5 (5.0 to 123.0)	87.0 (19.0 to 278.0)	40.0 (12.0 to 81.0)
	Not reported	3	1	3
Period 3: 0.120 mg/kg/day	Mean (SD)	56.9 (67.5)	100.4 (71.1)	42.6 (27.9)
	Median (min-max)	20.0 (10.0 to 232.0)	68.0 (24.0 to 238.0)	32.0 (13.0 to 101.0)
	Not reported	2	2	5
Change from baseline to period 1	Mean (SD)	2.5 (20.9)	-3.5 (36.6)	0.4 (20.8)
	Median (min-max)	1.0 (-26.0 to 49.0)	-16.0 (-73.0 to 70.0)	0.0 (-44.0 to 53.0)
	H-L (95% C.I.)*	0.5 (-9.0, 13.0)	-3.0 (-23.0, 16.0)	0.5 (-8.0, 8.5)
	Not reported	2	0	1
Change from baseline to period 2	Mean (SD)	15.9 (30.5)	31.7 (54.7)	-8.4 (14.4)
	Median (min-max)	11.0 (-29.0 to 91.0)	28.5 (-41.0 to 182.0)	-7.0 (-40.0 to 12.0)
	H-L (95% C.I.)*	15.0 (-1.5, 33.0)	24.0 (1.5, 54.5)	-7.0 (-16.5, 0.0)
	Not reported	3	1	3
Change from baseline to period 3	Mean (SD)	34.4 (61.4)	32.5 (63.7)	-3.0 (14.3)
	Median (min-max)	10.0 (-34.0 to 213.0)	9.0 (-36.0 to 176.0)	-1.5 (-27.0 to 20.0)
	H-L (95% C.I.)*	20.0 (1.5, 59.0)	21.0 (-5.0, 69.0)	-3.0 (-12.0, 6.0)
	Not reported	2	2	5

However, large confidence intervals suggested highly variable results. Examination of the individual data in all three studies failed to show any consistent dose-response relationship. The following figure examines the dose-response in the subjects of Study 001 and is representative of the dose-response relationship seen in all three studies.

Change from Baseline in Volume to First Detrusor Contraction; Individual Data from Study 001 (N=19)



PM = Poor metabolizer, ?? = not genotyped

This disparity between mean and individual results was generally caused by a small number of outliers (2-3) per treatment group that led to a skewing of the mean results.

Safety and Efficacy
The sponsor performed two phase 3 safety and efficacy trials. In both studies, no efficacy was demonstrated in treating 5-10 year olds with urge urinary incontinence with 2 mg daily of the MR formulation. For more information relevant to these studies, the reader is referred to the detailed medical review.

Population PK Analyses
Two population PK analyses were submitted by the sponsor. The first analysis involved modeling parent and metabolite concentrations using the data rich PK studies, 044 and 018. A three compartment model best fit the data. The following covariates were identified as contributing to the PK of tolterodine and DD01 in children; 2D6 phenotype, weight, height, gender, alpha$_1$ acid glycoprotein (AGP) and formulation/age. The last covariate's designation reflects the fact that the effect of age cannot be separated from the effect of formulation in this dataset because younger children were treated with the IR formulation and older children were treated with the MR formulation in Studies 018 and 044. Also age, weight, height and sex were found to be highly correlated.

The second analysis involved fitting the sparse PK data from the two phase 3 trials to the previously developed model. The new data allowed partial separation of the variables of age and formulation and found race also plays a significant role in the PK characteristics of tolterodine and DD01. Further analysis of the phase 3 data suggests that mean active moiety AUC was lower than that achieved in adults.

This lower observed exposure may have resulted from some assumptions made by the sponsor in the tolterodine pediatric development program. The sponsor assumed that the IR liquid used in the PK studies would result in similar exposures to that achieved with the same dose of the IR tablet. They also assumed that children would, like adults, experience similar active moiety exposures at a stable dose of tolterodine, whether administered in the IR or MR formulation. That stable dose/formulation/exposure relationship has not been demonstrated in children.

Overall Conclusion

In the following pediatric development process the sponsor selected doses to study in children based on an assumption that drug exposures associated with effective doses in adults would yield efficacy in the pediatric population. The sponsor conducted initial pediatric PK studies to determine the dose that yielded these adult exposures, but subsequent PK/PD studies in children did not show a response and no efficacy was demonstrated in 2 Phase 3 trials.

The doses selected for testing efficacy in the 2 phase 3 trials might have been different had the sponsor first performed PK/PD studies to determine the exposure associated with adequate response and then performed PK studies to determine the dose in children required to achieve these exposures. The efficacy data, however, that were presented in this application do not support use of tolterodine for treatment of children.

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/s/

Daniel A. Shames

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Clinical Pharmacology and Biopharmaceutics Review

NDA	21,228/20,771
Submission Date	October 10, 2003
Brand Name	Detrol and Detrol LA
Generic Name	Tolterodine tartrate
Primary Reviewer	Stephan R. Ortiz, R.Ph., Ph.D.
Pharmacometrics Reviewer	He Sun, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Pfizer
Submission Type; Code	Pediatric Exclusivity Submission; 3S
Dosing regimen	Daily or BID
Indication	Treatment of urge urinary incontinence

The briefing held May 19, 2004, was attended by the following: John Hunt, Don Stanski, Chandra Sahajwalla, Arzu Selen, Brenda Gierhart, Lisa Soule, Myong Jin Kim, Sandhya Apparaju and Albert Perrine.

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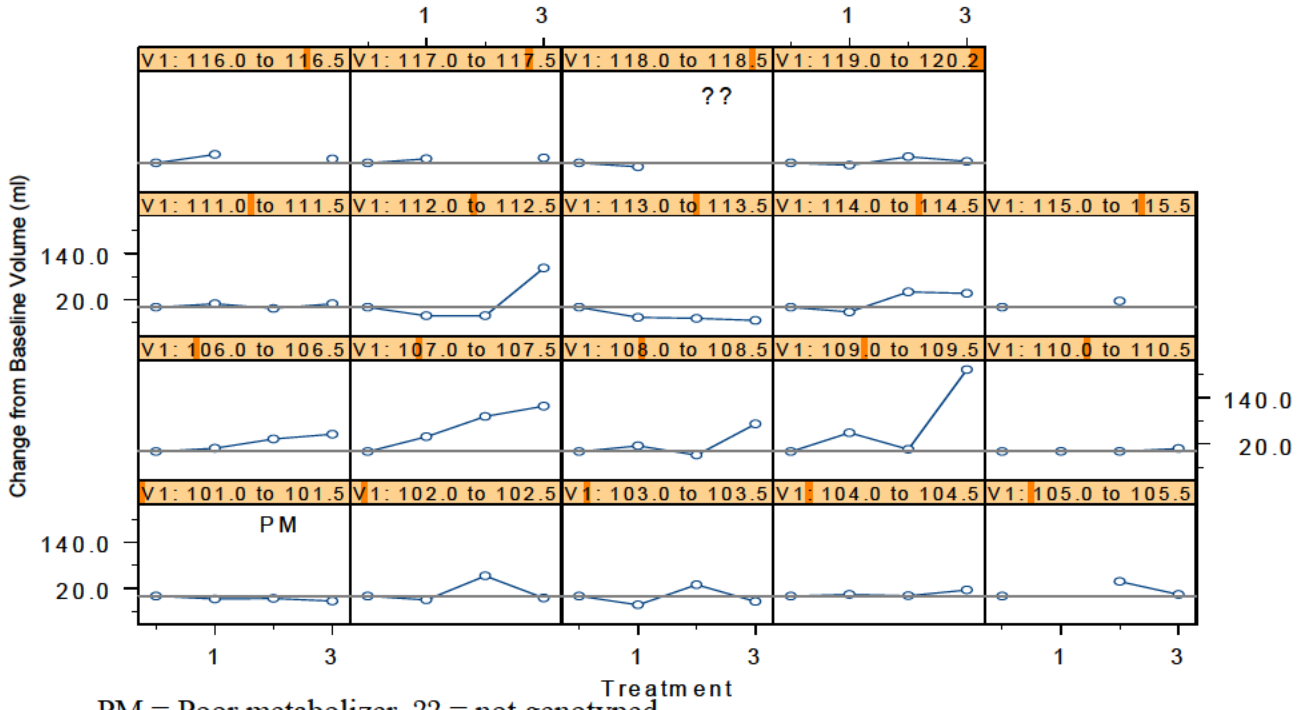

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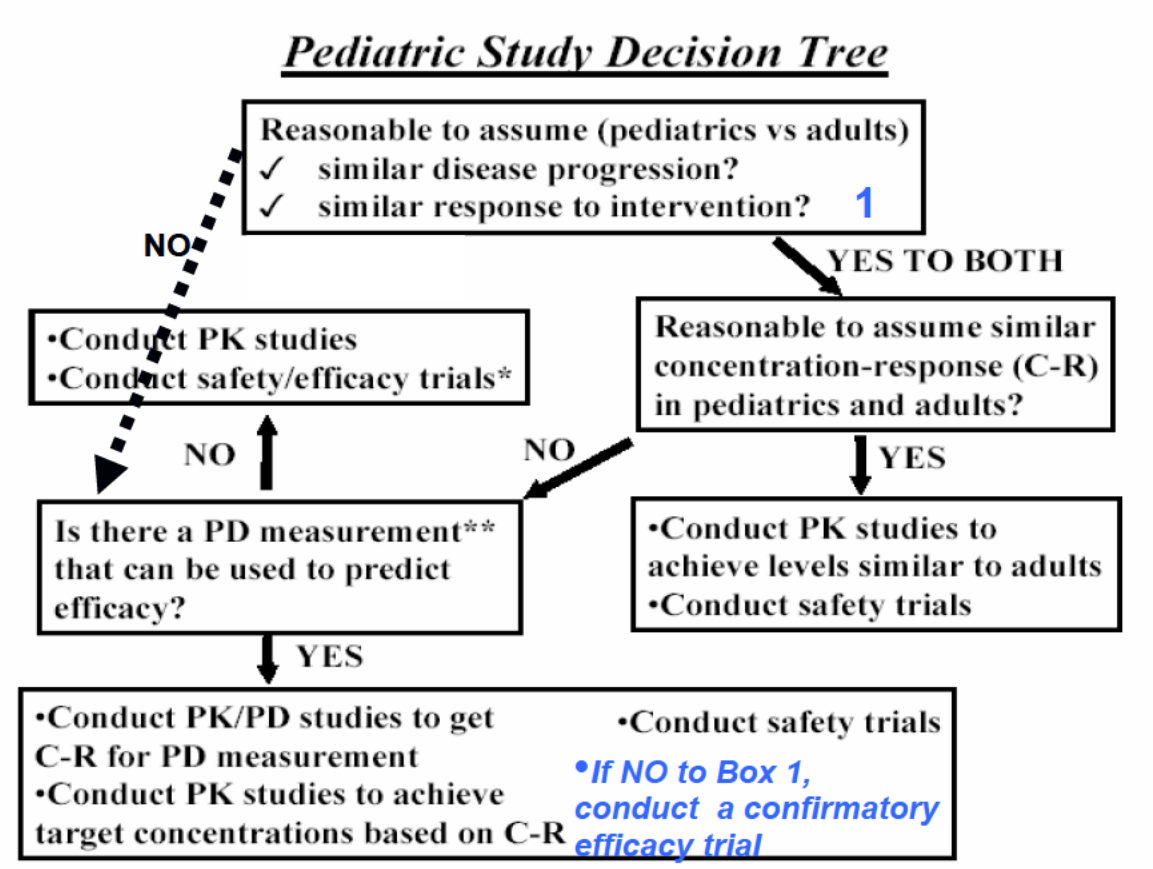
This lower observed exposure may have resulted from some assumptions made by the sponsor in the tolterodine pediatric development program. The sponsor assumed that the IR liquid used in the PK studies would result in similar exposures to that achieved with the same dose of the IR tablet. They also assumed that children would, like adults, experience similar active moiety exposures at a stable dose of tolterodine, whether administered in the IR or MR formulation. That stable dose/formulation/exposure relationship has not been demonstrated in children.

Overall Conclusion
In the following pediatric development process the sponsor selected doses to study in children based on an assumption that drug exposures associated with effective doses in adults would yield efficacy in the pediatric population. The sponsor conducted initial pediatric PK studies to determine the dose that yielded these adult exposures, but subsequent PK/PD studies in children did not show a response and no efficacy was demonstrated in 2 Phase 3 trials.

The doses selected for testing efficacy in the 2 phase 3 trials might have been different had the sponsor first performed PK/PD studies to determine the exposure associated with adequate response and then performed PK studies to determine the dose in children required to achieve these exposures. The efficacy data, however, that were presented in this application do not support use of tolterodine for treatment of children.

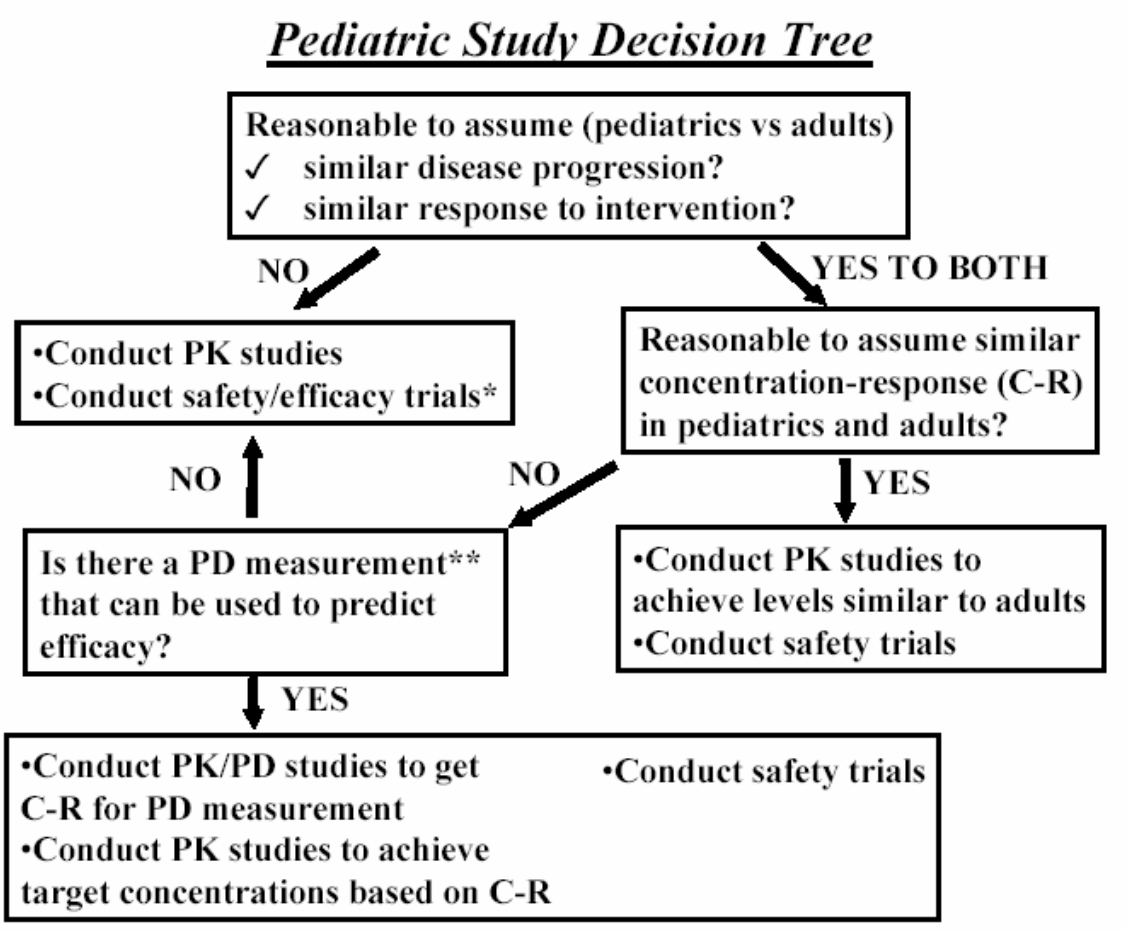
In attempting to utilize the Pediatric Decision Tree, several discussions arose regarding potential modifications based on the results of this submission. As a result of these discussions, the following modifications were suggested. These modifications should not be construed as official changes to the current pediatric decision tree, as seen on the following page.



A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the information included in the sNDA and has found it to be acceptable. PK was adequately characterized; however, tolterodine use was not shown efficacious in the pediatric population.

B. Current Pediatric Study Decision Tree



Indication: Detrol and Detrol LA capsules are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

1. Is it reasonable to assume that pediatric patients are similar to adults with regard to disease progression?

- Currently, the pediatric population is treated with the same therapeutic class, muscarinic blocker, as adults in the treatment of overactive bladder. However, it is not uncommon to treat pediatric patients with higher exposures during treatment. Thus, it is not reasonable to assume that pediatric patients are similar to adults with regard to disease progression.

2. Is it reasonable to assume that pediatric patients are similar to adults with regard to response to intervention?

- Clinicians currently use another marketed muscarinic blocker in the treatment of overactive bladder. It seems reasonable to assume that the response to disease intervention would be similar.

The Pediatric Study Decision Tree suggests:
- Conducting PK studies
- Conducting safety and efficacy trials

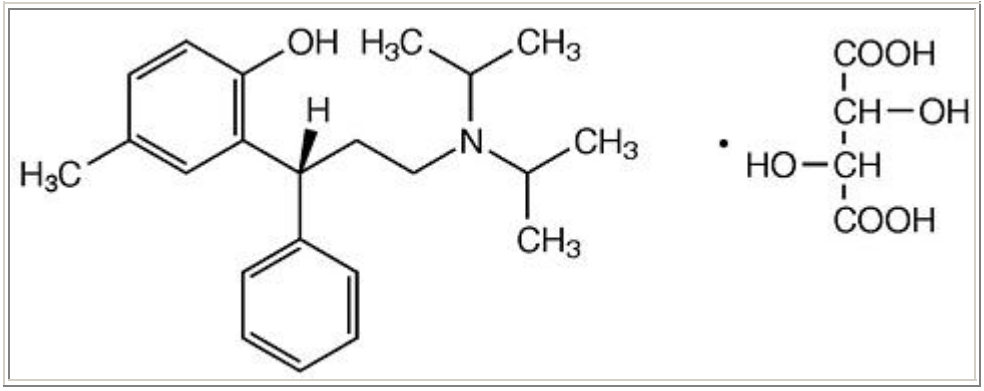
These studies were performed by the sponsor.

3 Question Based Review

A. General Attributes

What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

The active moiety of both Detrol and Detrol LA, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_7$, and its molecular weight is 475.6. The structural formula of tolterodine tartrate is represented below.



Tolterodine tartrate is a white, crystalline powder. The pKa value is 9.87 and the solubility in water is 12 mg/mL. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3.

DETROL Tablets for oral administration contain 1 or 2 mg of tolterodine tartrate. The inactive ingredients are colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, hydroxypropyl methylcellulose, magnesium stearate, sodium starch glycolate (pH 3.0 to 5.0), stearic acid, and titanium dioxide.

DETROL LA for oral administration contains 2 mg or 4 mg of tolterodine tartrate. Inactive ingredients are sucrose, starch, hypromellose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, and FD&C Blue #2. The 2-mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.

What is the approved dose in adults?

In adults, the doses are 1 and 2 mg BID IR and 2 and 4 mg QD MR.

What is the proposed mechanism of drug action and therapeutic indications?
Normal bladder contractions are mediated primarily through cholinergic muscarinic receptor stimulation. These receptors are believed to control normal bladder contractions, and possibly play a major role in overactive bladders. Hence, antimuscarinic drugs have become a standard of therapy for overactive bladder. However, a common side effect of this class of drugs is dry mouth (due to its effect on the salivary glands) and other anticholinergic effects.

Tolterodine is a potent competitive muscarinic antagonist exhibiting some selectivity towards antimuscarinic activity at the bladder (in animal models). The FDA approved tolterodine tartrate immediate release (IR) formulation at 1 and 2 mg BID doses in 1998 and tolterodine tartrate extended release capsule 2 and 4 mg once daily, both for the management of overactive bladder. The current application seeks pediatric exclusivity of both Detrol and Detrol LA in the pediatric population.

B. General Clinical Pharmacology

Were appropriate clinical endpoints, surrogate endpoints or pharmacodynamic (PD) biomarkers selected, adequately measured and used to assess efficacy and safety in clinical pharmacology studies?
Assorted studies were submitted by the sponsor in an attempt to determine safety and efficacy of tolterodine tartrate in the pediatric population. PD endpoints among the studies included mean number of daily micturitions, residual volume and number of incontinence episodes per week. PK parameters included AUC_{0-24} for both tolterodine and the active metabolite (DD01), C_{max} for the active moiety (sum of unbound tolterodine and DD01), tolterodine and DD01 and t_{max} and $t_{1/2}$ for tolterodine and DD01. Safety markers included clinical chemistry, hematology, urinalyses, urine residual volume, ECG, and spontaneous adverse event (AE) reporting.

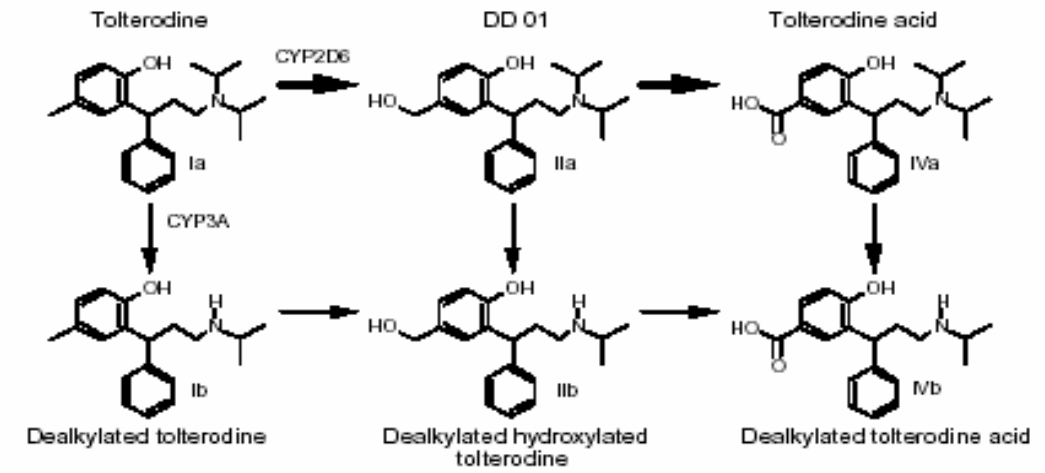
Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
Yes, both tolterodine and DD01 concentrations were determined by a validated LC-MS/MS assay. The assay validation was acceptable.

Was a mass balance determination performed?
Mass balance determinations were not performed in this submission. However, in the original submission for detrol (NDA 20,771), following administration of a 5-mg IR oral dose of ^{14}C-tolterodine to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces. Less than 1% (<2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (<1% in poor metabolizers) was recovered as the active 5-hydroxymethyl metabolite.

What is the metabolic pathway of the drug?

The metabolism of tolterodine is shown in the following figure.

Metabolic Scheme of tolterodine



Tolterodine is highly and selectively biotransformed by cytochrome P450 (CYP) 2D6, a polymorphically distributed isoenzyme, to the pharmacologically active 5-hydroxymethyl metabolite (DD 01). This metabolite is mainly responsible for the effect in extensive metabolizers. CYP2D6 is absent in approximately 7% of the Caucasian population as a result of mutations in the CYP2D6 gene. In previous phase II and III studies on tolterodine the patients have not been genotyped or phenotyped with regard to this deficiency. Genotyping was, however, done in these trials.

The samples were screened for the presence of the wild type CYP2D6 allele (CYP2D6*1) and the following variant alleles: CYP2D6*3, *4, *5, *6, *7, *8 and *2xN. In addition, samples from Oriental subjects was to be screened for the CYP2D6*10 allele and samples from black subjects for the CYP2D6*17 allele. Samples from any subject that were initially characterized as *4/*1 were also to be screened for the CYP2D6*10 allele since the assay did not have the specificity to detect a *4/*10 combination. Subjects were classified as homozygous or heterozygous extensive metabolizers.

Samples were processed for CYP2D6 *3, *4, *6, *7, and *8 alleles by multiplex polymerase chain reaction. For the multiplex and *17 assays, a first round amplification generated templates for use with allele specific primer sets. The *10 assay utilized allele specific primers which amplified directly from genomic DNA. The *2xN and *5 assays were performed using amplification of specific primers through long-range PCR.

The elimination half-life of tolterodine has been estimated at 2-3 hours in extensive metabolizers and about 10 hours in poor metabolizers. The accumulation of tolterodine and DD 01 in serum is low after doses of 2 and 4 mg bid of Detrol in both poor and extensive metabolizers.

How much of the drug is bound to plasma proteins?

Tolterodine and DD 01 are bound to orosomucoid (α_1-acid glycoprotein, AGP). The protein binding of tolterodine in serum is relatively high (unbound fraction 3.7%), while DD 01 has a low binding (unbound fraction 36%)

How were the doses chosen for the clinical trials?
Results from a PK study in 5-10 year olds showed that exposure in children at the 1 mg BID (IR) dose corresponds to that seen in adults at 2 mg BID (IR). It was concluded that based on these findings, the safe and effective dose of tolterodine in the 5-10 year age group would be 1 mg BID. However, another PK study in 11-15 year olds showed that the exposure resulting from 4 mg MR QD in children and adults was similar. In adults, results from a large, international phase III study showed that exposure resulting from a 4 mg QD dose of the MR formulation corresponds to the exposure that results from 2 mg BID of the IR formulation.
Using these results, the sponsor proceeded to Phase III in children with the 2 mg QD of the MR formulation. Analysis of the PK/PD results suggests that this may not have been the appropriate dose.

1. Pharmacokinetics

This submission contains 2 pharmacokinetic studies. The first studies the safety and PK of assorted doses of the immediate release (IR) formulation in 5-10 year olds. The second studies the safety and PK of assorted doses of the prolonged release (MR) formulation in 11-15 year olds.

(i) Study 044 was an open, uncontrolled, dose escalating study conducted to determine the safety and PK of multiple doses of tolterodine (IR). The study was to examine 0.5, 1, 2 and 3mg BID administration in patients between 5 and 10 years of age after oral administration for 14 days. The primary endpoint was the residual volume, which was not to exceed 20 mL after two weeks of administration. Additionally, blood was sampled for genotyping and PK assessment of tolterodine and its main metabolite, DD01. A total of 33 children were analyzed, divided into 3 groups; the 3 mg BID dose treatment group was terminated due to a surpassing of a pre-specified exposure limit.

Venous blood samples of 2 mL were drawn prior to and at 0.5, 1, 2 and 3 hours after the first tolterodine dose on day 1 and prior to and at 0.5, 1, 2, 3, 4, 6 and 8 hours after the last tolterodine dose on day 14. Venous blood was also drawn for AGP and for purposes of genotyping CYP2D6.

The following tables describe the demographics from the assorted treatment groups studied and the PK parameters of tolterodine and its metabolites after the first dose on day 1.

Demographic variables (mean, range) of included patients

	0.5 mg bid	1 mg bid	2 mg bid
No. of subjects included	11	10	12
Sex	9M/2F	5M/5F	6M/6F
Genotype/Phenotype	10 EM and 1 PM	10 EM and 0 PM	10 EM and 2 PM
Age (years)	7.4 (5–10)	7.4 (5-10)	7.4 (5-10)
Body weight (Kg)	25.8 (20.0-35.0)	27.8 (20.0-39.0)	27.0 (17.0-38.5)
Height (cm)	124.5 (112–147)	126.2 (114-144)	124.4 (110-145)

M = males, F = females, EM = extensive metaboliser, PM = poor metaboliser

C_{max} (mcg/mL) (mean ± SD) for tolterodine and its metabolites after the first dose of tolterodine on day 1, EM patients

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	2.6±2.1 n=10[a]	5.7±4.6 n=10	9.3±5.3 n=10[b]
DD 01	1.7±1.1 n=10	4.0±2.7 n=10	6.1±3.6 n=10
Dealkylated hydroxylated tolterodine	0.31±0.0.8 n=5	0.47±0.18 n=10	1.3±0.6 n=10[c]
Tolterodine acid	3.3±1.9 n=10	6.3±3.5 n=10	10.6±6.4 n=10[d]
Dealkylated tolterodine acid	1.5±1.0 n=10	2.6±1.0 n=10	5.0±2.9 n=10[e]

Cmax for PM patients: [a] No. 9 = 2.5; [b] Nos. 29 and 30 = 41.2 and 68.3; [c] Nos. 29 and 30 = <LOQ, 0.5; [d] Nos. 29 and 30 = <LOQ, 0.5;[e] Nos. 29 and 30 = <LOQ, 0.5

The following tables show the C_{max}, AUC_{0-12}, t_{max} and $t_{1/2}$ of tolterodine and its metabolites after the tolterodine dose on day 14.

Cmax (mcg/mL) (mean ± SD) for tolterodine and its metabolites after the first dose of tolterodine on day 14, EM patients

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	3.4 ± 3.0 n = 9[a]	4.9 ± 2.9 n = 10	11.5 ± 6.5 n = 9[b]
DD 01	2.0 ± 0.9 n = 9	4.6 ± 1.7 n = 10	8.5 ± 4.0 n = 9
Dealkylated hydroxylated tolterodine	0.3 ± 0.1 n = 6	0.7 ± 0.3 n = 9	1.8 ± 0.9 n = 9
Tolterodine acid	3.6 ± 1.7 n = 9	7.5 ± 2.9 n = 10	13.0 ± 4.9 n = 9
Dealkylated tolterodine acid	1.9 ± 0.8 n = 9	3.3 ± 0.8 n = 10	6.6 ± 2.3 n = 10[c]

PM patients: [a]No. 9 Cmax = 6.8; [b] No. 29 Cmax = 41.6; [c]No. 29 Cmax = 0.3

AUC_{0-12} (mcg*h/mL) (mean ± SD) for tolterodine and its metabolites after the first dose of tolterodine on day 14, EM patients

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	11.2 ± 13.5 n = 9[a]	14.8 ± 10.2 n = 10	31.7 ± 16.3 n = 9[b]
DD 01	7.6 ± 2.5 n = 9	17.4 ± 8.3 n = 10	34.1 ± 12.0 n = 9
Dealkylated hydroxylated tolterodine	‡ n = 2	3.1 ± 0.6 n = 8	8.7 ± 3.5 n = 9
Tolterodine acid	20.7 ± 4.9 n = 9	39.4 ± 8.9 n = 10	77.1 ± 25.3 n = 9
Dealkylated tolterodine acid	12.0 ± 4.2 n = 9	21.0 ± 3.1 n = 10	48.2 ± 12.5 n = 8

‡ 2.6 and 2.8 µg·h /L

PM patients: [a]No. 9 AUC = 61; [b]No. 29 AUC = 211;

T_{max} (h) (mean ± SD) for tolterodine and its metabolites after the first dose of tolterodine on day 14, EM patients

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	1.4 ± 0.9	1.2 ± 0.6	1.3 ± 0.7
	n = 9[a]	n = 10	n = 9[b]
DD 01	1.5 ± 0.8	1.6 ± 0.6	1.6 ± 0.6
	n = 9	n = 10	n = 9
Dealkylated hydroxylated tolterodine	1.9 ± 0.8	1.8 ± 0.6	1.9 ± 0.9
	n = 6	n = 9	n = 9
Tolterodine acid	2.7 ± 1.1	2.3 ± 0.9	2.7 ± 0.7
	n = 9	n = 10	n = 9[c]
Dealkylated tolterodine acid	2.9 ± 1.6	2.6 ± 0.7	2.8 ± 0.9
	n = 9	n = 10	n = 10

PM patients: [a]No. 9 Tmax = 4.1; [b]No. 29 Tmax = 1; [c]No. 29 Tmax = 3.0;

$T_{1/2}$ (h) (mean ± SD) for tolterodine and its metabolites after the first dose of tolterodine on day 14, EM patients

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	1.8 ± 1.1	1.4 ± 0.4	2.0 ± 0.8
	n = 9[a]	n = 10	n = 9[b]
DD 01	2.6 ± 1.3	2.1 ± 0.3	2.6 ± 1.0
	n = 9	n = 10	n = 9
Dealkylated hydroxylated tolterodine	‡	2.8 ± 1.0	3.4 ± 2.1
	n = 2	n = 8	n = 9
Tolterodine acid	3.3 ± 1.5	3.0 ± 1.0	3.5 ± 1.2
	n = 8	n = 10	n = 9
Dealkylated tolterodine acid	4.1 ± 2.0	4.3 ± 1.7	4.3 ± 1.3
	n = 7	n = 10	n = 8

‡ 5.4 and 10 h

PM patients: [a]No. 9 t1/2 = 11; [b]No. 29 t1/2 = 3.2;

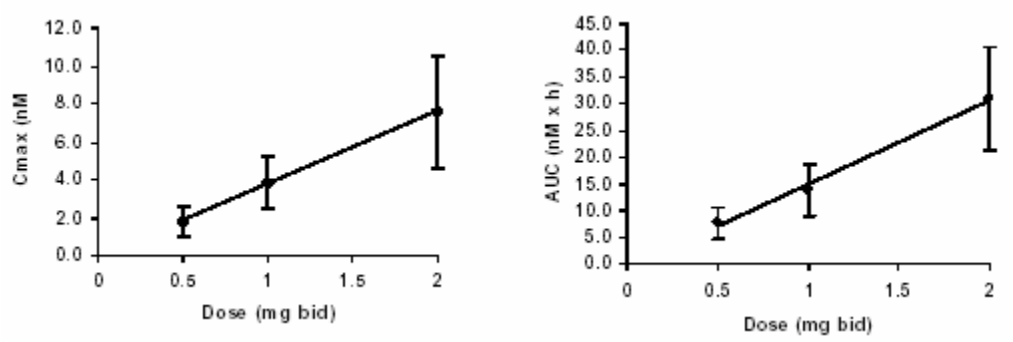
The degree of accumulation in extensive metabolizers based on Cmax values on day 14 and day 1 can be estimated to be about 1.1 -1.3 for tolterodine and its metabolites.

The sponsor defines the active moiety as the sum of the unbound fractions of tolterodine and DD01. Mean values for $C_{max,u}$ and AUC_u for the different treatment groups is presented in the following table and shown graphically in the following figure.

$C_{max,u}$ and AUC_u (mean ± SD) of active moiety (EM and PM patients)

	0.5 mg bid	1 mg bid	2 mg bid
Cmax (nM)	1.8 ± 0.8	3.9 ± 1.4	7.6 ± 3.0
AUC (nM ·h)	7.2 ± 2.4	13.9 ± 4.9	30.9 ± 9.7

Figure ??. $C_{max,u}$ and AUC_u (mean ± SD) of active moiety



Reviewer's Comments:

- Mean $C_{max,u}$ and AUC_u of active moiety increased linearly within the dose interval studied.
- The AUC_{0-12} did not increase linearly though this may be due to the high variability seen in the 0.5mg BID group. AUC_{0-12} of DD01 did increase linearly with dose.
- The degree of accumulation in extensive metabolizers based on C_{max} values on day 14 and day 1 can be estimated to be about 1.1 -1.3 for tolterodine and DD 01.
- The sponsor compared the results of this study with results obtained in adult studies. Based on the following table, the sponsor suggests the preferred dose of 1 mg BID for the treatment of children aged 5-10 years.
- The one PM subject in this study showed similar active moiety exposure to the EM subjects.

$C_{max,u}$ and AUC_u (mean ± SD) of active moiety in children at 1 mg BID and adults at 2 mg BID

Parameter	Children, 1 mg bid (n=10)	Adults[1], 2 mg bid (n=24)	Adults[2], 2 mg bid (n=18)
Cmax (nM)	3.9 ± 1.4	3.4 ± 1.7	2.8 ± 0.82
AUC (nM·h)	14 ± 4.9	14 ± 6.4	15 ± 4.3

[1] Brynne and Holgersson 1999 [2] Hallén et al 1997

(ii) Study 018 was a multicenter, open, sequential, dose-escalating trial determining the PK and safety of tolterodine (MR) 2 and 4 mg once daily for 6-10 days in children 11 through 15 years of age. The primary objective of this study was to collect data as a basis for a dosage recommendation for tolterodine in children 11 through 15 years of age, based primarily on a comparison of the exposure to the active moiety (sum of unbound tolterodine and DD 01) with data from studies in adults, and in children 5 through 10 years of age. The primary endpoint was AUC_{0-24} for the active moiety. Secondary objectives were to study pharmacokinetic variables for tolterodine and DD 01, C_{max} for the active moiety, and the effect and safety of tolterodine (MR), given as 2- and 4-mg once daily doses for seven days, in patients from 11 through 15 years of age.

Venous blood samples of 3 mL for determination of tolterodine and DD 01 were drawn predose (maximum 10 minutes before) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, and 25 hours post-dose on the PK Day. The exact time point for sampling was recorded in the CRF. Venous blood was also drawn for AGP and for purposes of genotyping CYP2D6, as described earlier.

The following tables list the PK variable estimates for tolterodine, DD01 and the active moiety.

Pharmacokinetic variables for tolterodine in EM and PM subjects

Variable		Treatment: 2-mg dose, Extensive Metabolizer N=7	Treatment: 2-mg dose, Poor Metabolizer N=2	Treatment: 4-mg dose, Extensive Metabolizer N=20
AUC0-24 (µg·h/L)	Mean (SD)	39.4 (37.5)	210.5 (18.6)	42.8 (34.2)
	Median (min-max)	25.6 (2.5 - 108.5)	210.5 (197.3 - 223.7)	31.0 (8.7 - 123.8)
Cmax (µg/L)	Mean (SD)	3.22 (2.94)	10.76 (2.74)	3.43 (2.60)
	Median (min-max)	1.91 (0.35 - 8.34)	10.76 (8.82 - 12.70)	2.58 (0.56 - 9.87)
Tmax (h)	Mean (SD)	3.57 (1.28)	3.51 (0.72)	3.85 (1.57)
	Median (min-max)	3.00 (1.98 - 6.00)	3.51 (3.00 - 4.02)	3.53 (1.95 - 6.97)
t½ (h)	Mean (SD)	13.6 (4.5)	165.6 (161.4)	16.6 (13.4)
	Median (min-max)	14.2 (5.4 - 17.7)	165.6 (51.5 - 279.8)	9.9 (5.8 - 52.7)
Vss/F (L)	Mean (SD)	1204 (1366)	145 (26)	1492 (1223)
	Median (min-max)	637 (195 - 4031)	145 (127 - 163)	922 (224 - 4304)
Cl/F (L/h)	Mean (SD)	103.6 (185.0)	1.06 (0.92)	81.2 (66.6)
	Median (min-max)	39.5 (7.9 - 520.1)	1.06 (0.40 - 1.71)	65.3 (10.9 - 234.7)

Reviewers comment:

- The high $t_{1/2}$ seen with the PM subgroup is the result of 1 subject's very high estimate. Analysis of the individual data shows a lack of points to characterize the terminal phase leading to an unreasonably high estimate of the half-life. The second subject had a half-life of 46 hours.

Pharmacokinetic variables for DD01 in EM subjects

Variable		Treatment: 2-mg dose, Extensive Metabolizer N=7	Treatment: 4-mg dose, Extensive Metabolizer N=20
AUC0-24 (µg·h/L)	Mean (SD)	20.6 (9.2)	32.9 (11.6)
	Median (min-max)	18.5 (7.2 - 34.4)	31.0 (18.5 - 54.1)
Cmax (µg/L)	Mean (SD)	1.33 (0.56)	2.38 (1.01)
	Median (min-max)	1.26 (0.71 - 2.43)	2.38 (1.04 - 5.44)
Tmax (h)	Mean (SD)	4.71 (1.25)	5.00 (2.02)
	Median (min-max)	4.00 (3.00 - 6.00)	5.05 (1.97 - 9.00)
t½ (h)	Mean (SD)	14.8 (3.2)	15.3 (11.5)
	Median (min-max)	13.6 (11.6 - 19.6)	13.0 (6.4 - 51.4)

Pharmacokinetic variables for the active moiety in all patients

Variable		Treatment			
		2-mg dose			4-mg dose
		Extensive Metabolizer N=7	Poor Metabolizer N=2	All N=9	Extensive Metabolizer N=20
AUC0-24 (nM·h)	Mean (SD)	17.3 (6.0)	12.3 (0.2)	16.2 (5.6)	29.7 (11.1)
	Median (min-max)	17.4 (7.5 - 24.7)	12.3 (12.2 - 12.5)	16.2 (7.5 – 27.7)	26.7 (14.4 -52.3)
Cmax (nM)	Mean (SD)	1.23 (0.33)	0.62 (0.09)	1.10 (0.39)	2.17 (0.95)
	Median (min-max)	1.34 (0.75 - 1.57)	0.62 (0.56 - 0.69)	1.19 (0.56 – 1.57)	2.07 (0.93 - 5.25)

Reviewer's Comments:

- The PK estimates for the extensive metabolizer subgroup appear to not be dose-linear for C_{max} or AUC over the doses studied for tolterodine or DD01.
- Subsequent plotting of C_{max} and AUC of the active moiety vs. patients' age, vs. body weight and vs. BMI showed no apparent relationship with age and a negative correlation with body weight and BMI. The variability between patients, however, was considerable.

Tolterodine is a basic amine that has high serum protein binding (primarily to α_1-acid glycoprotein (AGP) and is extensively metabolized to DD 01 during first-pass by CYP2D6. In poor metabolizers (devoid of CYP2D6) DD 01 is not formed. However, previous studies in adults have shown that the effect is related to the sum of unbound concentrations of tolterodine and DD 01 (active moiety) which is similar in extensive and poor metabolizers. In the comparison of exposure to the active moiety, between the patients in this study and healthy volunteers or patients in previous studies, all patients (EMs and PMs) were included. The exposure (AUC_u) to the active moiety in this study, 30.5 ± 11.0 nM·h, is comparable to the average exposure in adults after administration of 4 mg MR capsules, but higher than the average exposure in adults after administration of IR tablets. Data are compiled in the table below. In children 5-10 years old, the exposure to the active moiety (AUC_{0-12}) was 7.2±2.4, 13.9±4.9, and 30.9±9.7 nM·h after the 0.5, 1, and 2 mg b.i.d. doses of the IR tablet, respectviely. The 1-mg bid dosage in children 5-10 years of age gave similar exposure as 2-mg bid dosage in adults.

C_{max} at steady state after treatment with the MR capsule has only been determined in one study in adults. It was 2.3 (± 1.0) nM (range 0.77 – 3.7 nM). In the children 5-10 years old, C_{max} for the active moiety was 1.8±0.8, 3.9±1.4, and 7.6±3.0 nM after the 0.5, 1, and 2 mg BID doses of the IR tablet, respectively. C_{max} at steady state of the active moiety in this study is comparable to the results obtained in adults after administration of the MR capsule.

AUC and C_{max} of active moiety in children and adults

Variable		PR capsule		IR tablet	
		Children[1] *4 mg N=29	Adults[2] 4 mg N=17	Adults[3] *4 mg N=183	Children[4] 2 mg b.i.d. N=10
AUC0-24 (nM·h)	Mean (SD)	30.50 (11.00)	30.4 (13.7)	24.7 (8.8)	‡30.9 (9.7)
Cmax (nM)	Mean (SD)	2.18 (0.89)	2.3 (1.0)	-	7.6 (3.0)

[1]This study, [2][13], [3][16], [4][12], *Normalized to correspond 4 mg, ‡ (AUC0-12)

Reviewer's Comments:

- The exposure in terms of the sum of unbound tolterodine and DD 01(AUCu) at the dose of 4 mg (MR) was found to be comparable to that observed previously in adults given 4 mg (MR) once daily.
- Based on the combined pharmacokinetic and safety data, the present study indicates that 4 mg (MR) once daily is safe for treatment of patients 11-15 years of age.

2. Exposure-Response

(i) Study 001 was an open label dose-escalation (using three doses), multi-center, pharmacokinetic, pharmacodynamic, clinical effect and safety study in the 1 month to 4 year age range conducted at eight centers in the US. Approximately 15 patients were to be included in the study, with at least three patients less than 6 months old, approximately 50% of the remaining 12 patients 6 months to 2 years of age, and the remaining 50% 2 to 4 years of age. This study used a tolterodine (IR) liquid preparation. Since this is not an approved product, BA/BE studies were performed.

Patients began treatment with tolterodine at 0.030 mg/kg/day, given in divided doses. After 4 weeks at 0.030 mg/kg/day and safety and efficacy assessments, the dose was then escalated to 0.060 mg/kg/day. And after 4 weeks at 0.060 mg/kg/day and safety and efficacy assessments, the dose was then escalated to 0.120 mg/kg/day. PK data was collected in each patient at the completion of the 0.060 mg/kg/day dosage level only. The primary objective of this study was to collect data to be used as a basis for a dosage recommendation for tolterodine in children 1 month through 4 years of age with neurogenic lower urinary tract dysfunction. This recommendation was primarily based on a comparison of the pharmacokinetics of the active moiety (defined as the sum of unbound tolterodine and DD 01) with data from studies in adults and children 5 through 10 years old.

Secondary objectives were to estimate the pharmacokinetic variables for tolterodine and DD 01, and to assess the pharmacodynamic (urodynamic) and clinical effects and safety of tolterodine oral solution given at doses of 0.030, 0.060, and 0.120 mg/kg/day in patients from 1 month through 4 years of age with neurogenic lower urinary tract dysfunction. Data were collected to determine the tolterodine dose-pharmacodynamic effect and the tolterodine/DD 01 (active moiety) concentration-pharmacodynamic effect relationship with the urinary storage parameters of volume and compliance.

Pharmacodynamic evaluations included:

- Volume to first detrusor contraction of magnitude >10 cm H2O pressure;
- Functional bladder capacity and leak point pressure;
- Intravesical volume at 20 and 30 cm H_2O pressure;
- Maximal cystometric capacity (intravesical volume at 40 cm H2O pressure);
- Bladder compliance, defined as Δ volume/Δ pressure.

Venous blood samples of 500 µL for the determination of tolterodine and DD 01 were to be drawn pre-dose (maximum 10 minutes before dosing) and at 0.5, 1, 2, 6, and 8 hours post-dose on the PK day (0.060 mg/kg/day). The exact time points for sampling were to be recorded in the CRF. Additionally, venous blood will be sampled for determinations of AGP concentrations and CYP2D6 genotype.

The frequency distribution of total daily dose by age group is provided in the following table.

Total Daily Dose of Tolterodine by Dose Period and Age Group (N=15)

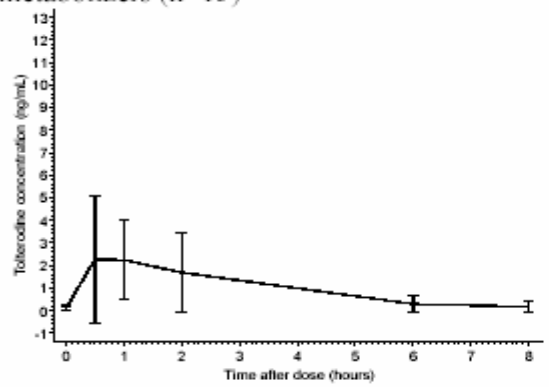
	Period 1 0.030 mg/kg/day (N=19)			Period 2 0.060 mg/kg/day (N=19)			Period 3 0.120 mg/kg/day (N=17)		
Total Daily Dose in mg:	<6 mos	6 mos to <2 yrs	2 to <5 yrs	<6 mos	6 mos to <2 yrs	2 to <5 yrs	<6 mos	6 mos to <2 yrs	2 to <5 yrs
<=0.2 mg	2	1	.	.	.	.	.	.	.
>0.2-0.5 mg	1	5	9	3	1	.	.	.	.
>0.5-1.0 mg	.	.	1	.	5	9	2	1	.
>1.0-2.0 mg	.	.	.	.	.	1	1	4	8
>2.0-3.0 mg	.	.	.	.	.	.	.	.	1
Mean (mg)	0.34			0.71			1.48		
Median (mg)	0.34			0.70			1.52		
Min, Max (mg)	0.16, 0.65			0.38, 1.31			0.80, 2.64		

Pharmacokinetics

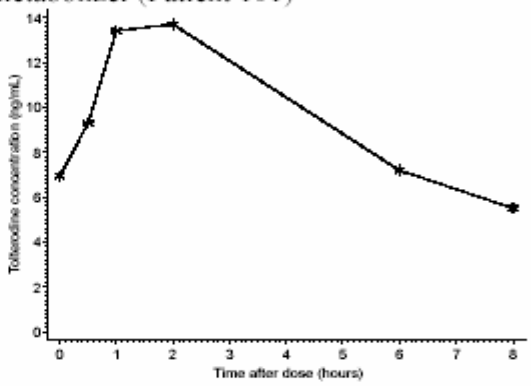
The mean PK profiles following 0.030 mg/kg bid are presented graphically in the following figure.

Mean (± SD) Concentrations after 0.030 mg/kg bid (0.060 mg/kg/day) dose

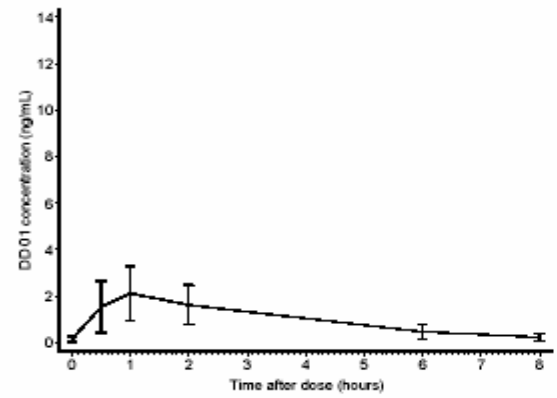
Tolterodine concentrations in extensive metabolizers (n=15)



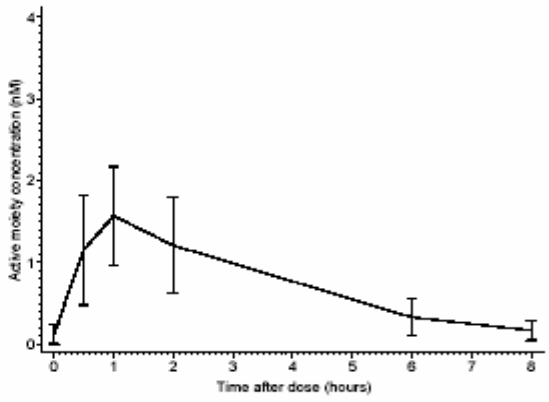
Tolterodine concentrations in the poor metabolizer (Patient 101)



DD 01 concentrations in extensive metabolizers, (n=15)



Active moiety concentrations for extensive and poor metabolizers, (n=16)



Reviewer's Comments:

- Inspection of the concentration-time profiles show that there was considerable inter-patient variability.
- Mean (SD) fu for tolterodine was 0.022 (0.007); the mean (SD) fu for DD01 was 0.26 (0.06).

Pharmacokinetic parameters for tolterodine, DD01 and the active moiety are presented in the following tables.

PK Parameters for the active moiety after the 0.030 mg/kg bid dose (0.060 mg/kg/day)

Parameter	Statistic	Active moiety
AUC_{0-12} (nM*hr)	Mean (SD)	5.9 (2.6)
	Median (min, max)	5.7 (2.9, 12.0)
F_{ext} (%)	Mean (SD)	6.7 (4.3)
	Median (min, max)	5.4 (2.0, 18.1)
C_{max} (nM)	Mean (SD)	1.66 (0.61)
	Median (min, max)	1.59 (0.82, 2.76)
C_{min} (nM)	Mean (SD)	0.08 (0.11)
	Median (min, max)	0.04 (0.00, 0.34)

PK Parameters for tolterodine and DD01 after the 0.030 mg/kg bid dose (0.060 mg/kg/day)

		Tolterodine		DD 01
Parameter	Statistic	Extensive Metabolizers (n=12)	Poor Metabolizers (n=1)	Extensive Metabolizers (n=15)
AUC_{0-12} (µg*hr/L)	Mean (SD) Median (min, max)	8.5 (8.0) 7.8 (1.4, 30.3)	92.4	7.9 (3.9) 8.5 (3.0, 15.6)
F_{ext} (%)	Mean (SD) Median (min, max)	3.2 (3.1) 2.1 (0.3, 8.8)	18.1	6.3 (3.4) 5.7 (2.1, 13.1)
C_{max} (µg/L)	Mean (SD) Median (min, max)	2.86 (2.75)* 2.49 (0.43, 10.40)*	13.70	2.23 (1.12) 2.17 (0.79, 5.13)
t_{max} (hr)	Mean (SD) Median (min, max)	1.02 (0.59)* 0.92 (0.47, 2.00)*	1.88	1.12 (0.53) 1.00 (0.47, 2.00)
C_{min} (µg/L)	Mean (SD) Median (min, max)	0.051 (0.102)* 0.000 (0.000, 0.360)*	5.510	0.071 (0.101) 0.000 (0.000, 0.317)
$t_{1/2,z}$(hr)	Mean (SD) Median (min, max)	1.52 (0.58) 1.34 (0.91, 2.55)	4.54	2.09 (0.55) 1.92 (1.44, 3.21)
V_{ss}/F (L)	Mean (SD) Median (min, max)	113 (93) 102 (19, 291)	19	NC
CL/F (L/hr)	Mean (SD) Median (min, max)	58 (50) 40 (6, 177)	3	NC
V_{ss}/F (L/kg)	Mean (SD) Median (min, max)	9.31 (7.19) 5.26 (2.01, 22.89)	1.53	NC
CL/F (L/hr/kg)	Mean (SD) Median (min, max)	4.91 (4.52) 2.66 (0.67, 14.24)	0.23	NC

A comparison of AUC_{0-12} and C_{max} between different pediatric populations is presented in the following table.

AUC_{0-12} and C_{max} of Active Moiety in Pediatric Patients

Parameter	Statistic	Tolterodine Oral Solution (0.030 mg/kg/bid) in Patients 1 mo to 4 yr (N=16)	Tolterodine IR Tablets (0.5 mg bid) in Patients 5 to 10 yr [10] (N=10)
AUC_{0-12} (nM*h)	Mean (SD)	5.9 (2.6)	7.2 (2.4)
	Median (min, max)	5.7 (2.9, 12.0)	7.8 (3.7, 9.7)
C_{max} (nM)	Mean (SD)	1.7 (0.6)	1.8 (0.8)
	Median (min, max)	1.6 (0.8, 2.8)	1.9 (0.4, 3.0)

Reviewers Comments:

- The C_{max} and AUC were lower in the 0.030 mg/kg bid dose in 1 mo – 4 year olds as compared to the 0.5 mg bid (IR) dose in 5 – 10 year olds. It should be noted that the 0.030 mg/kg bid dose averaged to 0.35 mg bid for this population.
- Drug exposure, as measured by the AUC and C_{max} of the active moiety, in 1-month-old to 4-year-old patients with detrusor hyperreflexia at the dose of 0.030 mg/kg bid (0.060 mg/kg/day) was similar to that observed previously in 5- to 10-year-old children with

overactive bladder receiving 0.5 mg tolterodine IR tablets bid, and slightly less than half that reported in adults receiving 2 mg tolterodine IR tablets twice daily.

Pharmacodynamics
All patients had at least some urodynamic data at all dose periods (with the exception of the two withdrawn patients); however, at a number of patient-dose periods, some measurements could not be determined or were missing. In particular, maximal cystometric capacity (i.e., intravesical volume at 40 cm H2O pressure) and bladder wall compliance at 0 to 40 cm H2O pressure were often undetermined due to the patient developing discomfort before 40 cm H2O pressure was reached. This resulted in termination of bladder filling before these measurements could be quantified.

In general, the small sample size and considerable inter-patient variability are reflected in the wide 95% confidence limits. Nevertheless, the data for some urodynamic parameters were suggestive of a dose effect, as detailed below. The following tables show the dose-response for those urodynamic parameters in which a mean dose-response is suggested.

Volume to First Detrusor Contraction, Functional Bladder Capacity and Leak Point Pressure (N=19)

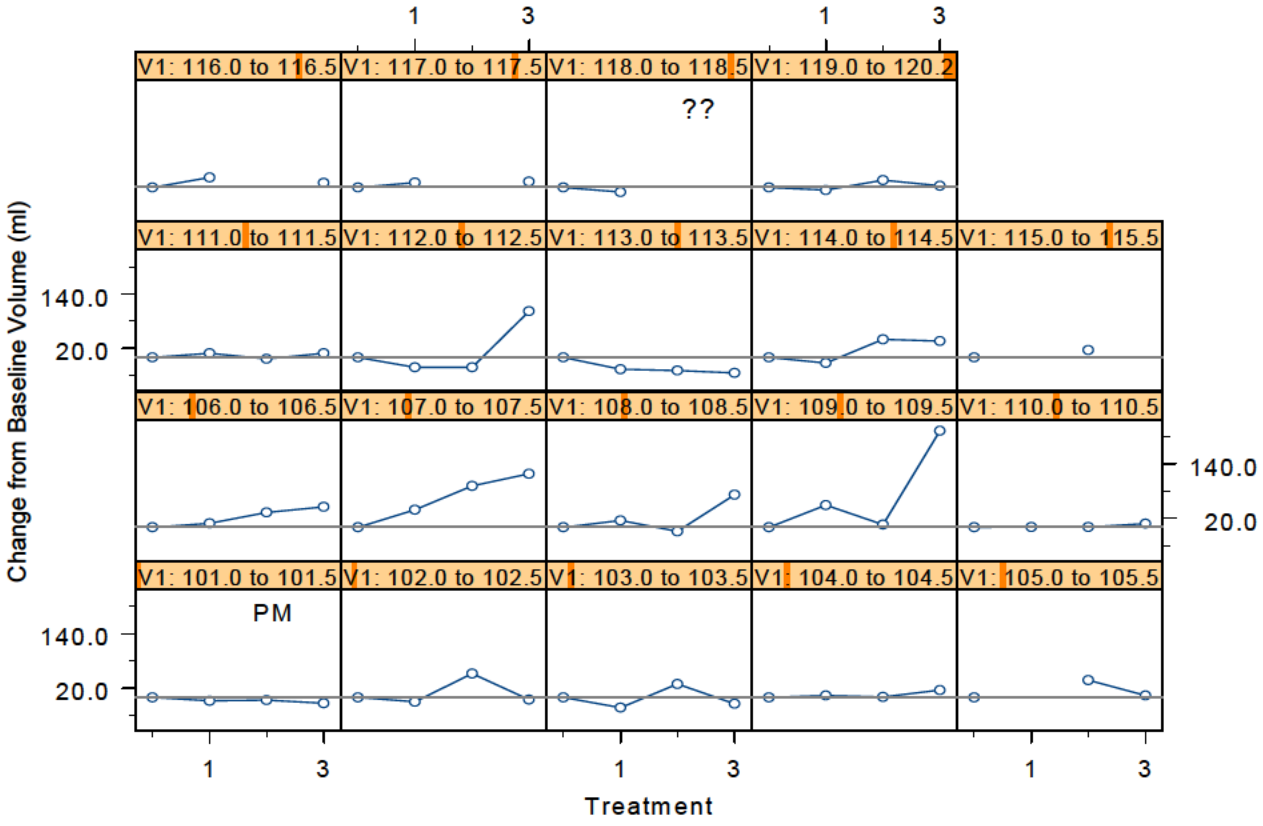
Dose Period	Statistic	Volume to first detrusor contraction of magnitude >10 cm H_2O pressure (mL)	Functional bladder capacity (mL)	Leak point pressure (cm H_2O)
Baseline	Mean (SD)	21.7 (16.6)	74.2 (41.5)	49.0 (21.3)
	Median (min-max)	15.0 (4.0 to 60.0)	62.0 (13.0 to 160.0)	48.0 (12.0 to 90.0)
	Not reported	0	0	0
Period 1: 0.030 mg/kg/day	Mean (SD)	25.5 (22.9)	70.7 (33.5)	50.5 (29.3)
	Median (min-max)	22.0 (3.0 to 71.0)	73.0 (15.0 to 136.0)	47.0 (10.0 to 113.0)
	Not reported	2	0	1
Period 2: 0.060 mg/kg/day	Mean (SD)	38.9 (29.7)	101.6 (67.5)	40.9 (21.4)
	Median (min-max)	31.5 (5.0 to 123.0)	87.0 (19.0 to 278.0)	40.0 (12.0 to 81.0)
	Not reported	3	1	3
Period 3: 0.120 mg/kg/day	Mean (SD)	56.9 (67.5)	100.4 (71.1)	42.6 (27.9)
	Median (min-max)	20.0 (10.0 to 232.0)	68.0 (24.0 to 238.0)	32.0 (13.0 to 101.0)
	Not reported	2	2	5
Change from baseline to period 1	Mean (SD)	2.5 (20.9)	-3.5 (36.6)	0.4 (20.8)
	Median (min-max)	1.0 (-26.0 to 49.0)	-16.0 (-73.0 to 70.0)	0.0 (-44.0 to 53.0)
	H-L (95% C.I.)*	0.5 (-9.0, 13.0)	-3.0 (-23.0, 16.0)	0.5 (-8.0, 8.5)
	Not reported	2	0	1
Change from baseline to period 2	Mean (SD)	15.9 (30.5)	31.7 (54.7)	-8.4 (14.4)
	Median (min-max)	11.0 (-29.0 to 91.0)	28.5 (-41.0 to 182.0)	-7.0 (-40.0 to 12.0)
	H-L (95% C.I.)*	15.0 (-1.5, 33.0)	24.0 (1.5, 54.5)	-7.0 (-16.5, 0.0)
	Not reported	3	1	3
Change from baseline to period 3	Mean (SD)	34.4 (61.4)	32.5 (63.7)	-3.0 (14.3)
	Median (min-max)	10.0 (-34.0 to 213.0)	9.0 (-36.0 to 176.0)	-1.5 (-27.0 to 20.0)
	H-L (95% C.I.)*	20.0 (1.5, 59.0)	21.0 (-5.0, 69.0)	-3.0 (-12.0, 6.0)
	Not reported	2	2	5

Reviewer comments:
- In examining the mean data, high variability is noted among the urodynamic variables, which warrants examination of individual patient data. Both non-normalized and normalized volume to first detrusor contraction data is presented below.

Volume to First Detrusor Contraction and Normalized Volume to First Detrusor Contraction (N=19)

Period	Variable	Volume to First Detrusor Contraction (ml)	Normalized Volume to First Detrusor Contraction (ml/kg)
Baseline	Mean (SD)	21.7 (16.6)	19.1 (16.62)
Change from Baseline to 0.03mg/kg/ day	Mean (95% CI)	2.5 (-9, 13)	-1.40 (-9.48, 8.11)
Change from Baseline to 0.06 mg/kg/ day	Mean (95% CI)	15.9 (-1.5, 33)	13.07 (0.45, 25.68)
Change from Baseline to 0.12 mg/kg/ day	Mean (95% CI)	34.4 (1.6, 59)	21.64 (2.50, 47.83)

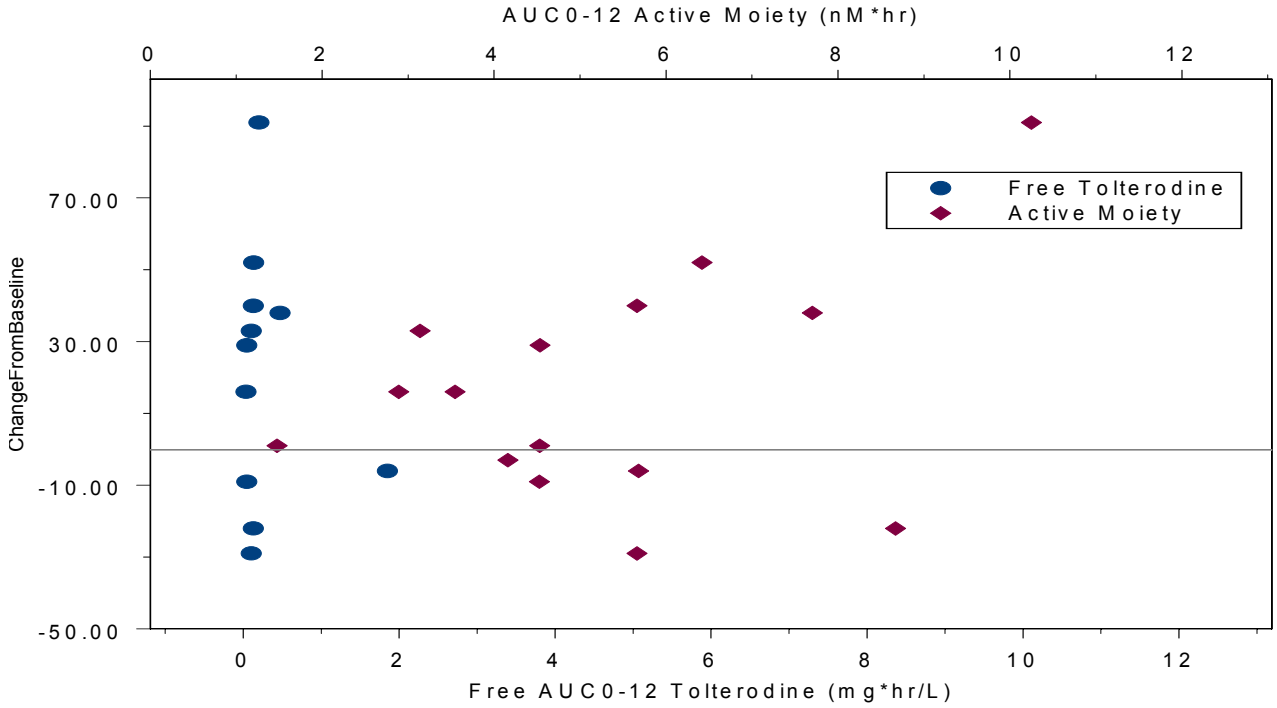
Change from Baseline in Volume to First Detrusor Contraction; Individual Data (N=19)



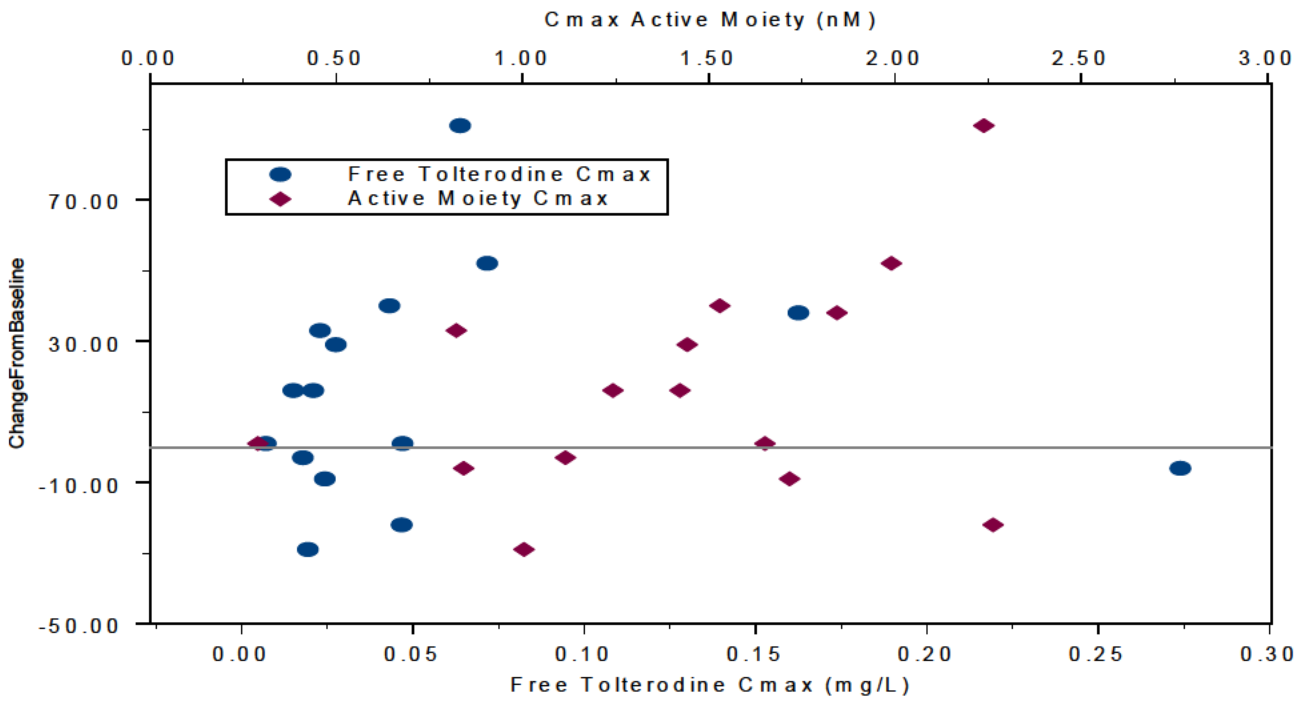
PM = Poor metabolizer
IM = Intermediate metabolizer
?? = not genotyped

Drug sampling was performed at the end of dosing for treatment group 2. Exposure-response analyses with both Cmax and AUC vs. change from baseline in treatment group 2 are presented in the next 2 figures.

Change from Baseline in Volume to First Detrusor Contraction vs. AUC of Free Tolterodine and Active Moiety (N=17)



Change from Baseline in Volume to First Detrusor Contraction vs. C_{max} of Free Tolterodine and Active Moiety (N=17)



Analysis of the individual data does not support the sponsor's assertion that a dose-response relationship exists. For example, the mean change from baseline of 34.4 ml as reported by the sponsor in treatment group 3 is largely attributed to 3 individual points of 102, 118 and 213 ml. Additionally, further analysis of potential covariates (age, race, sex) does not reveal a dose-response relationship.

Reviewers comments:

- Regarding the volume to first detrusor contraction data, examination of the data suggests no dose-response and limited efficacy in this age group.
- Functional bladder capacity showed similar mean increases from baseline at dose period 2 (31.7 [± 54.7] mL) and dose period 3 (32.5 [± 63.7] mL). Functional bladder capacity was essentially unchanged at dose period 1 (-3.5 [± 36.6] mL).
- Mean dose-related increases were seen for the volume to first detrusor contraction >10 cm H2O pressure: the largest mean change from baseline, +34.4 (±61.4) mL, was seen at dose period 3, and the next largest mean change, +15.9 (±30.5) mL, was seen at dose period 2. The volume to first detrusor contraction >10 cm H2O pressure was essentially unchanged at dose period 1 (+2.5 [±20.9] mL).
- In general, where a dose-effect was seen (upon analysis of mean data), the intermediate and highest doses (0.060 and 0.120 mg/kg/day) showed some improvements from baseline and were frequently of similar magnitude. Patients generally remained unchanged at the lowest dose (0.030 mg/kg/day).
- **It should be noted that the above mean differences are not supported by analysis of individual data. Overall, upon examination of individual data, efficacy has not been shown. Further, no age-, sex- or race-related trends were found.**

(ii) Study 002 was an open label dose-escalation (using three doses), multi-center, pharmacokinetic, pharmacodynamic, clinical effect and safety study in children with detrusor hyperreflexia 5-10 years of age. Approximately 15 patients were to be included in the study, with approximately one-half between 5-7 years of age and one-half between 8-10 years of age. This study was conducted in 14 centers in the United States; six centers enrolled patients. This study used a tolterodine (IR) liquid preparation.

Patients began treatment with tolterodine at 0.030 mg/kg/day, given in divided doses. After 4 weeks at 0.030 mg/kg/day and safety and efficacy assessments, the dose was then escalated to 0.060 mg/kg/day. And after 4 weeks at 0.060 mg/kg/day and safety and efficacy assessments, the dose was then escalated to 0.120 mg/kg/day. PK data was collected in each patient at the completion of the 0.060 mg/kg/day dosage level only.
The primary objective of this study was to collect data to be used as a basis for a dosage recommendation for tolterodine in children 5-10 years of age with neurogenic lower urinary tract dysfunction. This recommendation was based on a comparison of the pharmacokinetics of the active moiety (defined as the sum of unbound tolterodine and DD 01) with data from studies in adults and children 5 through 10 years old.

Secondary objectives were to estimate the pharmacokinetic variables for tolterodine and DD 01, and to assess the pharmacodynamic (urodynamic) and clinical effects and safety of tolterodine oral solution given at doses of 0.030, 0.060, and 0.120 mg/kg/day in patients from 1 month through 4 years of age with neurogenic lower urinary tract dysfunction. Data were collected to determine the tolterodine dose-pharmacodynamic effect and the tolterodine/DD 01 (active moiety) concentration-pharmacodynamic effect relationship with the urinary storage parameters of volume and compliance.

Pharmacodynamic evaluations included:
- Volume to first detrusor contraction of magnitude >10 cm H2O pressure;
- Functional bladder capacity and leak point pressure;
- Intravesical volume at 20 and 30 cm H_2O pressure;
- Maximal cystometric capacity (intravesical volume at 40 cm H2O pressure);
- Bladder compliance, defined as Δ volume/Δ pressure.

Venous blood samples of 500 μL for the determination of tolterodine and DD 01 were to be drawn pre-dose (maximum 10 minutes before dosing) and at 0.5, 1, 2, 6, and 8 hours post-dose on the PK day (0.060 mg/kg/day). The exact time points for sampling were to be recorded in the CRF. Additionally, venous blood will be sampled for determinations of AGP concentrations and CYP2D6 genotype.

The frequency distribution of total daily dose by age group is provided in the following table.

Total Daily Dose of Tolterodine by Dose Period and Age Group (N=15)

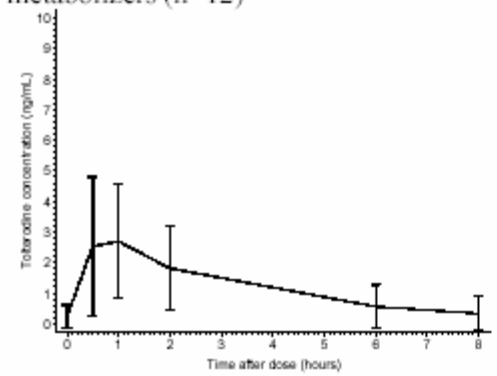
	Period 1 0.030 mg/kg/day (N=15)		Period 2 0.060 mg/kg/day (N=15)		Period 3 0.120 mg/kg/day (N=15)	
Total Daily Dose in mg:	5 to <8 years	8 to <11 years	5 to <8 years	8 to <11 years	5 to <8 years	8 to <11 years
0.2-0.5 mg	1	1	.	.	.	.
>0.5-1.0 mg	6	5	1	.	.	.
>1.0-2.0 mg	.	2	6	6	1	.
>2.0-3.0 mg	.	.	.	2	4	2
>3.0-4.0 mg	.	.	.	.	2	3
>4.0-5.0 mg	.	.	.	.	.	1
>5.0-6.0 mg	.	.	.	.	.	2
Mean (mg)	0.81		1.66		3.41	
Median (mg)	0.72		1.42		3.06	
Min, Max (mg)	0.49, 1.40		0.95, 2.95		1.92, 6.00	

Pharmacokinetics

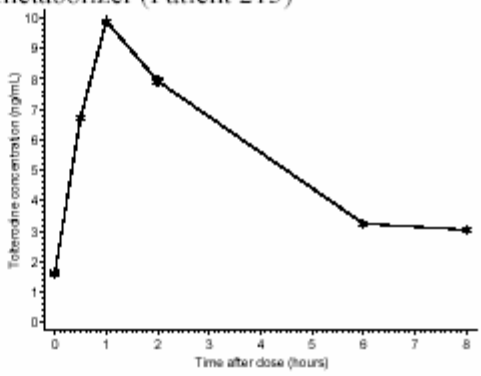
The mean PK profiles following 0.030 mg/kg bid are presented graphically in the following figure.

Mean (± SD) Concentrations after 0.030 mg/kg bid (0.060 mg/kg/day) dose

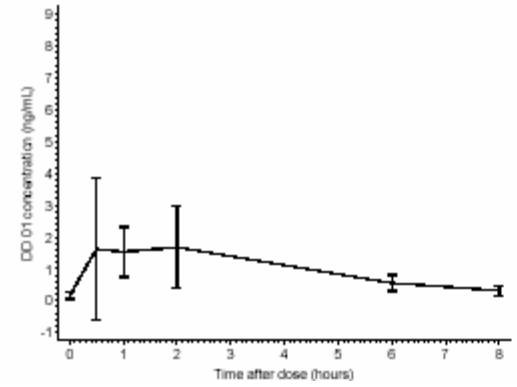
Tolterodine concentrations in extensive metabolizers (n=12)



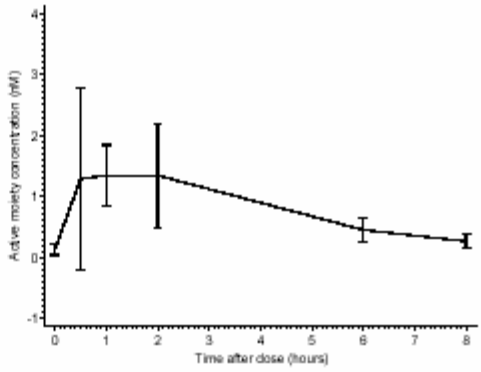
Tolterodine concentrations in the poor metabolizer (Patient 213)



DD 01 concentrations in extensive metabolizers (n=12)



Active moiety concentrations in extensive and poor metabolizers (n=13)



Mean PK parameters for tolterodine, DD01 and the active moiety are presented in the following tables.

PK Parameters for the active moiety after the 0.030 mg/kg bid dose (0.060 mg/kg/day) (N=13)

Parameter	Statistic	Active Moiety
$AUC_{0\text{-}12}$ (nM*hr)	Mean (SD)	7.4 (4.7)
	Median (min, max)	6.3 (4.3, 22.6)
F_{ext} (%)	Mean (SD)	9.9 (5.3)
	Median (min, max)	10.0 (2.4, 19.3)
C_{max} (nM)	Mean (SD)	1.78 (1.30)
	Median (min, max)	1.38 (0.79, 5.71)
C_{min} (nM)	Mean (SD)	0.10 (0.11)
	Median (min, max)	0.12 (0.00, 0.37)

PK Parameters for tolterodine and DD01 after the 0.030 mg/kg bid dose (0.060 mg/kg/day)

Parameter	Statistic	Tolterodine		DD 01
		Extensive Metabolizer (N=12)	Poor Metabolizer (N=1)	Extensive Metabolizer (N=12)
AUC_{0-12} (µg*hr/L)	Mean (SD)	10.4 (9.3)	50.5	9.1 (7.4)
	Median (min, max)	8.0 (1.5, 35.8)		7.4 (5.0, 32.0)
F_{ext} (%)	Mean (SD)	6.2 (5.1)	16.4	9.9 (5.5)
	Median (min, max)	4.2 (0.6, 16.9)		9.2 (2.7, 20.9)
C_{max} (µg/L)	Mean (SD)	3.28 (2.18)	9.88	2.18 (1.98)
	Median (min, max)	2.48 (0.64, 6.50)		1.50 (0.84, 7.93)
t_{max} (hr)	Mean (SD)	1.01 (0.53)	0.97	1.14 (0.57)
	Median (min, max)	1.00 (0.50, 2.05)		1.00 (0.50, 2.05)
C_{min} (µg/L)	Mean (SD)	0.17 (0.38)	1.62	0.12 (0.13)
	Median (min, max)	0.00 (0.00, 1.34)		0.13 (0.00, 0.41)
$t_{1/2,z}$ (hr)	Mean (SD)	2.20 (1.00)	3.88	3.01 (1.53)
	Median (min, max)	1.71 (1.05, 4.28)		2.78 (1.56, 7.21)
V_{ss}/F (L)	Mean (SD)	338 (407)	68	NC
	Median (min, max)	126 (66, 1268)		
CL/F (L/hr)	Mean (SD)	107 (128)	12	NC
	Median (min, max)	50 (19, 447)		
V_{ss}/F (L/kg)	Mean (SD)	10.95 (10.12)	2.30	NC
	Median (min, max)	6.54 (3.00, 30.72)		
CL/F (L/hr/kg)	Mean (SD)	3.71 (3.57)	0.41	NC
	Median (min, max)	2.61 (0.55, 13.76)		

Reviewers Comments:

- Mean active moiety PK parameters for the 0.030 mg/kg bid dose (i.e., the 0.060 mg/kg/day regimen) in this trial were more similar to those for the 0.5 mg than the 1 mg twice-daily tolterodine IR tablet dose in a previous study conducted in 5 to 10-year-old patients with overactive bladder (PK Study-044), despite the ~40% difference in dose.
- When comparing data from the present trial to adult PK parameters for the active moiety at a 2 mg bid dose, the average AUC and C_{max} for the 0.030 mg/kg bid dose in children (which averaged ~0.8 mg bid in the pediatric patients) was approximately half that in adults. This result was unexpected, since previous findings in this age group suggested that the 0.030 mg/kg bid dose in children would produce the same exposure as the 2 mg bid dose in adults. The following table compares the results of those studies performed in the 5-10 year age range.

AUC_{0-12} and C_{max} of Active Moiety in 5 to 10 year-old Patients

Para-meter	Statistic	Tolterodine Oral Solution 0.030 mg/kg bid N=13	Tolterodine IR Tablet [10] 0.5 mg bid N=10	Tolterodine IR Tablet [10] 1 mg bid N=10
AUC_{0-12}	Mean (SD)	7.4 (4.7)	7.2 (2.4)	13.9 (4.9)
(nM*hr)	Median (min, max)	6.3 (4.3, 22.6)	7.8 (3.7, 9.7)	13.0 (8.8, 25.0)
C_{max}	Mean (SD)	1.8 (1.3)	1.8 (0.8)	3.9 (1.4)
(nM)	Median (min, max)	1.4 (0.8, 5.7)	1.9 (0.4, 3.0)	3.6 (2.3, 6.2)

Pharmacodynamics

All patients had at least some urodynamic data at all dose periods (with the exception of Patient 209 at the first dose period); however, at a number of patient-dose periods, some measurements could not be determined or were missing. In particular, maximal cystometric capacity (i.e., intravesical volume at 40 cm H_2O pressure) and bladder wall compliance at 0 to 40 cm H_2O pressure were often undetermined due to the patient developing discomfort before 40 cm H_20 pressure was reached. This resulted in termination of bladder filling before these measurements could be quantified.

In general, the small sample size and considerable inter-patient variability are reflected in the wide 95% confidence limits. Nevertheless, the data for some urodynamic parameters were suggestive of a dose effect, as detailed below. The following tables show the dose-response for those urodynamic parameters in which a dose-response is suggested.

Volume to First Detrusor Contraction, Functional Bladder Capacity and Leak Point Pressure

Dose Period	Statistic	Volume to first detrusor contraction of magnitude >10 cm H_2O pressure (mL)	Functional bladder capacity (mL)	Leak point pressure (cm H_2O)
Baseline	Mean (SD)	38.4 (40.7)	119.7 (57.4)	45.6 (12.8)
	Median (min, max)	23.0 (5.0, 147.0)	121.0 (16.0, 200.0)	46.5 (20.0, 60.0)
	Not reported	1	0	3
Period 1: 0.030 mg/kg/day	Mean (SD)	49.2 (44.9)	156.6 (78.5)	42.8 (16.0)
	Median (min, max)	39.5 (5.0, 163.0)	174.0 (41.0, 273.0)	41.0 (19.0, 73.0)
	Not reported	3	1	2
Period 2: 0.060 mg/kg/day	Mean (SD)	58.8 (47.1)	156.9 (91.6)	59.3 (31.5)
	Median (min, max)	43.0 (14.0, 182.0)	144.0 (36.0, 313.0)	61.0 (12.0, 120.0)
	Not reported	2	1	6
Period 3: 0.120 mg/kg/day	Mean (SD)	73.4 (61.8)	182.2 (104.6)	47.9 (20.4)
	Median (min, max)	44.0 (11.0, 200.0)	200.0 (20.0, 364.0)	47.0 (10.0, 83.0)
	Not reported	2	2	6
Change from baseline to period 1	Mean (SD)	26.7 (40.3)	37.2 (69.8)	0.0 (8.4)
	Median (min, max)	25.0 (-11.0, 138.0)	25.0 (-92.0, 153.0)	-1.5 (-13.0, 13.0)
	H-L (95% C.I.)*	17.0 (3.5, 63.5)	31.0 (-4.0, 82.0)	0.0 (-7.0, 6.0)
	Not reported	4	1	5
Change from baseline to period 2	Mean (SD)	29.6 (42.3)	40.7 (82.0)	13.3 (28.6)
	Median (min, max)	19.0 (-10.0, 150.0)	15.5 (-60.0, 209.0)	10.0 (-13.0, 77.0)
	H-L (95% C.I.)*	20.8 (5.5, 46.5)	40.5 (-15.5, 90.0)	8.8 (-6.5, 45.5)
	Not reported	3	1	7
Change from baseline to period 3	Mean (SD)	37.0 (55.9)	65.0 (101.0)	2.6 (17.6)
	Median (min, max)	6.5 (-43.0, 158.0)	70.0 (-120.0, 234.0)	1.0 (-28.0, 27.0)
	H-L (95% C.I.)*	34.5 (5.0, 78.5)	66.0 (-1.5, 129.5)	1.5 (-14.0, 18.5)
	Not reported	3	2	7

Intravesical Volume (N=15)

Dose Period	Statistic	Intravesical volume at 20 cm H_2O pressure (mL)	Intravesical volume at 30 cm H_2O pressure (mL)	Intravesical volume at 40 cm H_2O pressure (mL)
Baseline	Mean (SD)	58.0 (59.2)	81.3 (69.3)	88.7 (66.4)
	Median (min, max)	35.0 (8.0, 195.0)	58.5 (10.0, 200.0)	86.5 (22.0, 186.0)
	Not reported	2	5	9
Period 1: 0.030 mg/kg/day	Mean (SD)	93.4 (60.6)	142.8 (84.5)	112.2 (61.3)
	Median (min, max)	76.0 (20.0, 200.0)	147.5 (30.0, 255.0)	90.0 (40.0, 187.0)
	Not reported	3	7	10
Period 2: 0.060 mg/kg/day	Mean (SD)	105.5 (57.1)	131.5 (65.5)	174.8 (100.4)
	Median (min, max)	105.0 (20.0, 225.0)	140.0 (22.0, 245.0)	182.0 (25.0, 346.0)
	Not reported	4	4	7
Period 3: 0.120 mg/kg/day	Mean (SD)	99.1 (68.7)	121.4 (78.0)	162.7 (93.3)
	Median (min, max)	88.0 (12.0, 215.0)	112.0 (16.0, 237.0)	191.0 (21.0, 287.0)
	Not reported	3	4	4
Change from baseline to period 1	Mean (SD)	26.9 (73.8)	65.3 (44.4)	21.8 (31.7)
	Median (min, max)	39.0 (-159.0, 126.0)	41.0 (20.0, 135.0)	19.5 (-10.0, 58.0)
	H-L (95% C.I.)*	38.0 (-27.0, 72.0)	63.8 (25.5, 122.0)	21.8 (-10.0, 58.0)
	Not reported	4	8	11
Change from baseline to period 2	Mean (SD)	35.2 (38.2)	33.9 (41.6)	49.0 (120.0)
	Median (min, max)	40.0 (-55.0, 80.0)	35.5 (-40.0, 97.0)	11.0 (-45.0, 219.0)
	H-L (95% C.I.)*	40.0 (5.0, 62.5)	34.8 (-3.0, 68.5)	29.0 (-45.0, 219.0)
	Not reported	5	7	11
Change from baseline to period 3	Mean (SD)	38.3 (83.6)	53.1 (90.6)	86.2 (94.4)
	Median (min, max)	52.5 (-183.0, 178.0)	80.0 (-150.0, 180.0)	99.0 (-29.0, 236.0)
	H-L (95% C.I.)*	46.3 (6.0, 79.0)	63.5 (-30.5, 113.5)	99.0 (-29.0, 236.0)
	Not reported	3	6	9

Bladder Wall Compliance (N=15)

Dose Period	Statistic	Bladder wall compliance 0-20 cm H_2O pressure (mL/cm H_2O)	Bladder wall compliance 0-30 cm H_2O pressure (mL/cm H_2O)	Bladder wall compliance 0-40 cm H_2O pressure (mL/cm H_2O)
Baseline	Mean (SD)	2.9 (3.0)	2.7 (2.3)	2.2 (1.7)
	Median (min, max)	1.8 (0.4, 9.8)	2.0 (0.3, 6.7)	2.2 (0.6, 4.7)
	Not reported	2	5	9
Period 1: 0.030 mg/kg/day	Mean (SD)	4.7 (3.0)	4.8 (2.8)	2.8 (1.5)
	Median (min, max)	3.8 (1.0, 10.0)	4.9 (1.0, 8.5)	2.3 (1.0, 4.7)
	Not reported	3	7	10
Period 2: 0.060 mg/kg/day	Mean (SD)	5.3 (2.9)	4.4 (2.2)	4.4 (2.5)
	Median (min, max)	5.3 (1.0, 11.3)	4.7 (0.7, 8.2)	4.6 (0.6, 8.7)
	Not reported	4	4	7
Period 3: 0.120 mg/kg/day	Mean (SD)	5.0 (3.4)	4.0 (2.6)	4.1 (2.3)
	Median (min, max)	4.4 (0.6, 10.8)	3.7 (0.5, 7.9)	4.8 (0.5, 7.2)
	Not reported	3	4	4
Change from baseline to period 1	Mean (SD)	1.3 (3.7)	2.2 (1.5)	0.5 (0.8)
	Median (min, max)	2.0 (-8.0, 6.3)	1.4 (0.7, 4.5)	0.5 (-0.3, 1.5)
	H-L (95% C.I.)*	1.9 (-1.3, 3.6)	2.1 (0.9, 4.1)	0.5 (-0.3, 1.5)
	Not reported	4	8	11
Change from baseline to period 2	Mean (SD)	1.8 (1.9)	1.1 (1.4)	1.2 (3.0)
	Median (min, max)	2.0 (-2.8, 4.0)	1.2 (-1.3, 3.2)	0.3 (-1.1, 5.5)
	H-L (95% C.I.)*	2.0 (0.3, 3.1)	1.2 (-0.1, 2.3)	0.7 (-1.1, 5.5)
	Not reported	5	7	11
Change from baseline to period 3	Mean (SD)	1.9 (4.2)	1.8 (3.0)	2.2 (2.4)
	Median (min, max)	2.6 (-9.2, 8.9)	2.7 (-5.0, 6.0)	2.5 (-0.7, 5.9)
	H-L (95% C.I.)*	2.3 (0.3, 4.0)	2.1 (-1.0, 3.8)	2.5 (-0.7, 5.9)
	Not reported	3	6	9

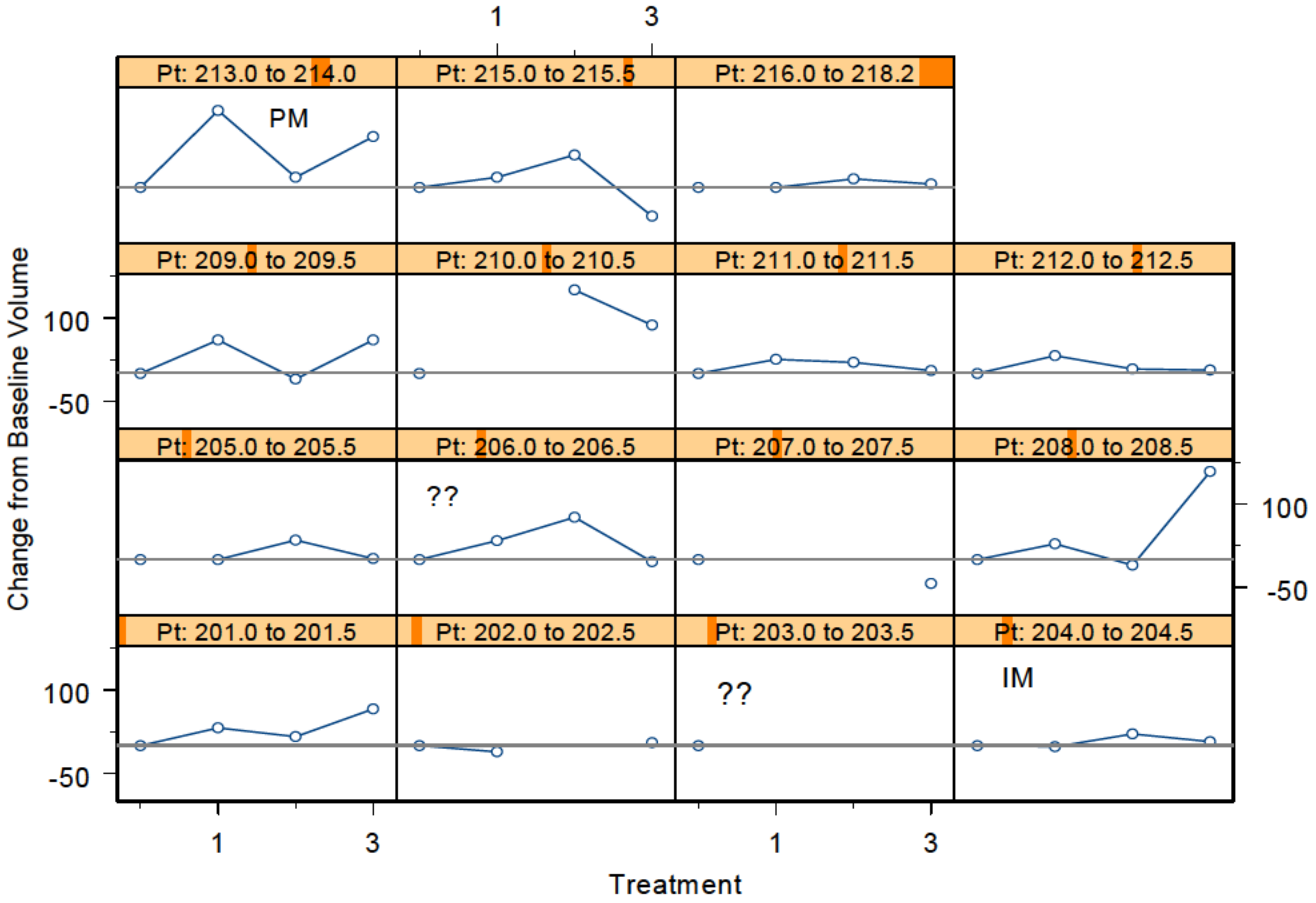
The high inter-patient variability warrants examination of the individual PD data. Both non-normalized and normalized volume to first detrusor contraction data is presented below. Individual plots of the data follow.

Volume to First Detrusor Contraction and Normalized Volume to First Detrusor Contraction (N=19)

Period	Variable	Volume to First Detrusor Contraction	Normalized Volume to First Detrusor Contraction
Baseline	**Mean (SD)**	**38.4 (40.7)**	**13.3 (13.55)**
Change from Baseline to 0.03mg/kg/ day	**Mean (95% CI)**	**17 (3.5, 63.5)**	**10.7 (3.7, 27.7)**
Change from Baseline to 0.06 mg/kg/ day	**Mean (95% CI)**	**20.8 (5.5, 46.5)**	**12.2 (2.3, 29.6)**
Change from Baseline to	**Mean (95% CI)**	**34.5 (5, 78.5)**	**11.4 (-0.1, 24.89)**

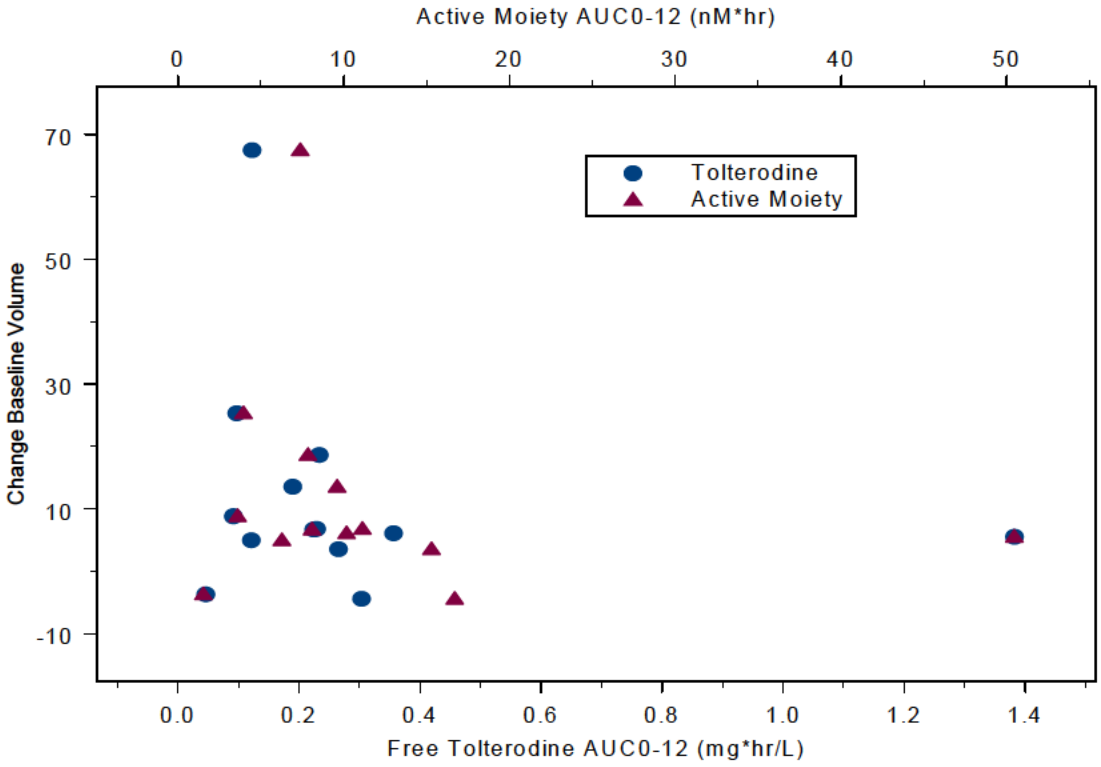
0.12 mg/kg/ day			

Change from Baseline in Volume to First Detrusor Contraction; Individual Data (N=15)

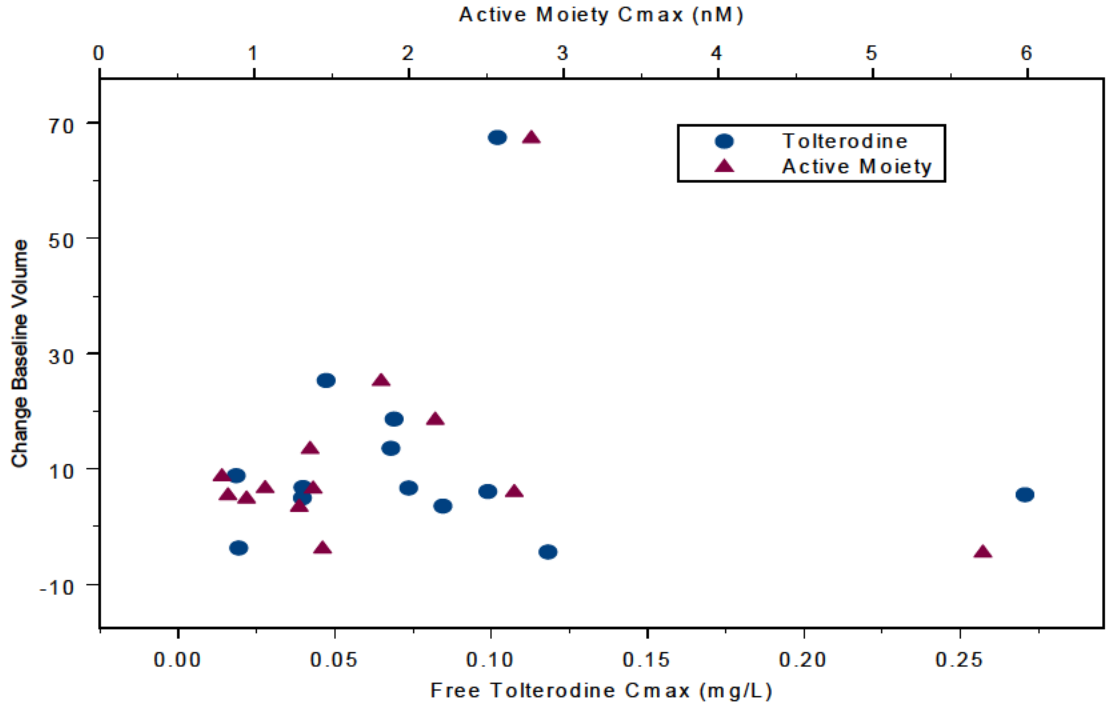


PM = Poor metabolizer
IM = Intermediate metabolizer
?? = not genotyped

Change from Baseline in Volume to First Detrusor Contraction vs. AUC of Free Tolterodine and Active Moiety (N=17)



Change from Baseline in Volume to First Detrusor Contraction vs. C_{max} of Free Tolterodine and Active Moiety (N=17)



Reviewers Comments:

- Functional bladder capacity showed similar mean increases from baseline at dose period 1 (+37.2 [± 69.8] mL) and dose period 2 (+40.7 [± 82.0] mL), and showed a larger increase at dose period 3 (+65.0 [± 101.0] mL).
- Intravesical volume at 20 cm H_20 pressure showed mean dose-related increases from baseline. This was also true for intravesical volume at 40 cm H_20 pressure (maximal cystometric capacity); however, these results should be interpreted with caution due to the number of missing values at each dose period (at least 9 of 15 patients missing change from baseline at each dose period). For intravesical volume at 30 cm H_20 pressure, the largest increases were seen at dose period 1 and dose period 3; however, due to the number of missing values, these results should also be interpreted cautiously.
- Mean dose-related increases in bladder wall compliance from 0 to 20 cm H_20 pressure were seen. For bladder wall compliance from 0 to 30 cm H_20 pressure, the largest increases were seen at dose period 1 and dose period 3. Due to the number of missing values, these results should be interpreted cautiously. Dose-related increases in bladder wall compliance from 0 to 40 cm H_20 pressure (i.e., defining maximal cystometric capacity) were seen; however, these results should also be interpreted with caution due to the large number of missing values.
- In general, where a mean dose-effect was seen, the lowest and intermediate doses (0.030 and 0.060 mg/kg/day) showed some improvements from baseline and were of similar magnitude, and the largest effect was seen at the highest dose (0.120 mg/kg/day).
- **It should be noted that the mean results noted above are not supported by analysis of individual data. Overall, upon examination of individual data, efficacy has not been shown nor has a dose-response relationship been established. Further, no age-, sex- or race-related trends were found.**

(iii) Study 003 was an open label dose-escalation (using three doses), multi-center, pharmacokinetic, pharmacodynamic, clinical effect and safety study of tolterodine MR capsules in children with detrusor hyperreflexia 11-15 years of age. Approximately 11 patients were to be included in the study, with approximately 60% between 11-13 years of age and the other 40% between 14-15 years of age. This study was conducted in 14 centers in the United States; six centers enrolled patients.

Patients began treatment with tolterodine at 2 mg/day, as a single daily dose. After 4 weeks at 2 mg/day and safety and efficacy assessments, the dose was then escalated to 4 mg/day. And after 4 weeks at 4 mg/day and safety and efficacy assessments, the dose was then escalated to 6 mg/day. PK data was collected in each patient at the completion of the 4 mg/day dosage level only.
The primary objective of this study was to collect data to be used as a basis for a dosage recommendation for tolterodine in children 11-15 years of age with neurogenic lower urinary tract dysfunction. This recommendation was based on a comparison of the pharmacokinetics of the active moiety (defined as the sum of unbound tolterodine and DD 01) with data from studies in adults and children 5 through 15 years old.

Secondary objectives were to estimate the pharmacokinetic variables for tolterodine and

DD 01, and to assess the pharmacodynamic (urodynamic) and clinical effects and safety of tolterodine oral solution given at doses of 2, 4 and 6 mg/day in patients from 11-15 years of age with neurogenic lower urinary tract dysfunction. Data were collected to determine the tolterodine dose-pharmacodynamic effect and the tolterodine/DD 01 (active moiety) concentration-pharmacodynamic effect relationship with the urinary storage parameters of volume and compliance.

Pharmacodynamic evaluations included:

- Volume to first detrusor contraction of magnitude >10 cm H2O pressure;
- Functional bladder capacity and leak point pressure;
- Intravesical volume at 20 and 30 cm H_2O pressure;
- Maximal cystometric capacity (intravesical volume at 40 cm H2O pressure);
- Bladder compliance, defined as Δ volume/Δ pressure.

Venous blood samples of 500 µL for the determination of tolterodine and DD 01 were to be drawn pre-dose (maximum 10 minutes before dosing) and at 0.5, 1, 2, 6, and 8 hours post-dose on the PK day (0.060 mg/kg/day). The exact time points for sampling were to be recorded in the CRF. Additionally, venous blood will be sampled for determinations of AGP concentrations and CYP2D6 genotype.

The frequency distribution of total daily dose by age group is provided in the following table.

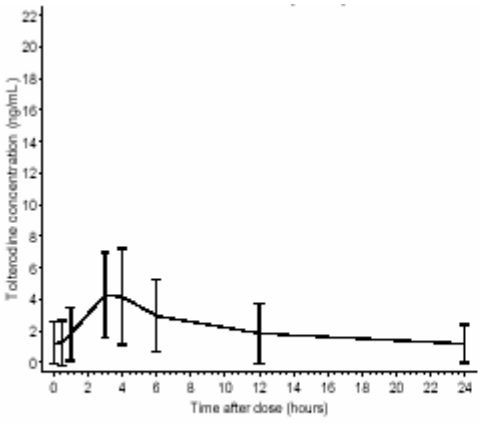
Total Daily Dose of Tolterodine by Dose Period and Age Group (N=11)

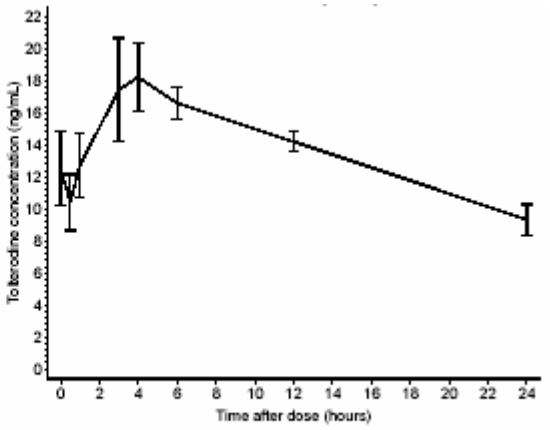
	Period 1, 2 mg/day (N=11)		Period 2, 4 mg/day (N=11)		Period 3, 6 mg/day (N=10)	
Total Daily Dose (mg/kg/day)	11 to < 14 years	14 to <16 years	11 to <14 years	14 to <16 years	11 to <14 years	14 to <16 years
>0.01-0.05	7	2	.	.	.	.
>0.05-0.10	1	1	7	2	2	1
>0.10-0.15	.	.	1	1	5	.
>0.15-0.20	.	.	.	.	1	1
Mean (mg/kg/day)	0.04		0.08		0.12	
Median (Min, Max) (mg/kg/day)	0.04 (0.03, 0.07)		0.07 (0.05, 0.14)		0.11 (0.08, 0.20)	

Pharmacokinetics

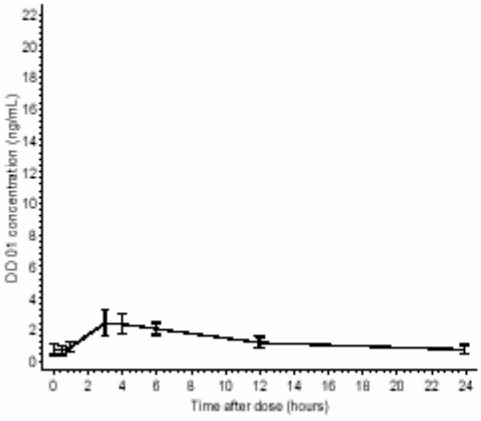
The mean PK profiles following 0.030 mg/kg bid are presented graphically in the following figure.

Mean (± SD) Steady-State Concentrations after the 4 mg/day Dose

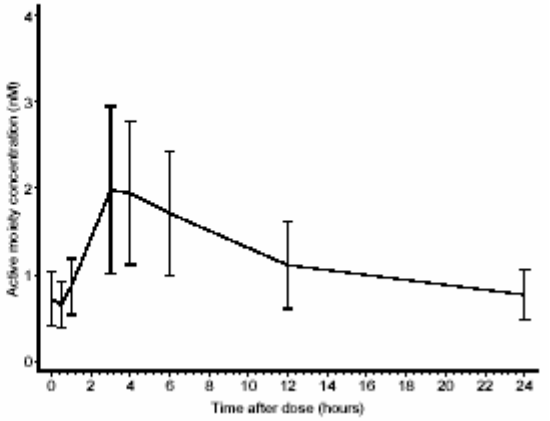




DD 01 concentrations in extensive metabolizers (n=7)



Active moiety concentrations in extensive and poor metabolizers (n=10)



Mean PK parameters for tolterodine, DD01 and the active moiety are presented in the following tables.

PK Parameters for the Active Moiety after the 4 mg/day Dose (N=10)

Parameter	Statistic	Active Moiety N=10
AUC_{0-24}(nM*hr)	Mean (SD)	27.3 (10.5)
	Median (min, max)	25.5 (11.5, 43.4)
C_{max} (nM)	Mean (SD)	2.10 (0.93)
	Median (min, max)	1.89 (1.03, 3.86)
C_{min} (nM)	Mean (SD)	0.619 (0.272)
	Median (min, max)	0.599 (0.237, 1.233)

PK Parameters for Tolterodine and DD01 after the 4 mg/day Regimen

Parameter	Statistic	Tolterodine Extensive Metabolizer N=7	Tolterodine Poor Metabolizer N=3	DD 01 Extensive Metabolizer N=7
AUC_{0-24} (µg*hr/L)	Mean (SD)	48.3 (41.1)	331.5 (19.8)	30.5 (6.0)
	Median (min, max)	31.2 (8.0, 129.8)	326.1 (315.0, 353.5)	32.7 (20.0, 36.9)
C_{max} (µg/L)	Mean (SD)	4.63 (3.01)	18.77 (1.42)	2.58 (0.72)
	Median (min, max)	3.93 (0.69, 8.77)	18.00 (17.90, 20.40)	2.43 (1.80, 3.89)
t_{max}(hr)	Mean (SD)	3.29 (0.49)	3.30 (0.61)	3.86 (1.07)
	Median (min, max)	3.00 (3.00, 4.00)	3.00 (2.90, 4.00)	4.00 (3.00, 6.00)
C_{min} (µg/L)	Mean (SD)	0.980 (0.938)	9.723 (1.973)	0.646 (0.320)
	Median (min, max)	0.677 (0.204, 2.980)	8.650 (8.520, 12.000)	0.572 (0.363, 1.190)
$t_{1/2,z}$(hr)	Mean (SD)	8.86 (4.00)	28.89 (10.72)	11.38 (8.03)
	Median (min, max)	8.53 (3.67, 13.44)	25.74 (20.10, 40.84)	9.46 (3.40, 28.04)
V_{ss}/F(L)	Mean (SD)	1530 (2081)	344 (112)	NC
	Median (min, max)	672 (297, 6129)	323 (243, 465)	
CL/F(L/hr)	Mean (SD)	110 (109)	8 (0)	NC
	Median (min, max)	88 (21, 344)	8 (8, 9)	
V_{ss}/F(L/kg)	Mean (SD)	29.62 (39.38)	5.77 (2.02)	NC
	Median (min, max)	15.94 (7.72, 117.86)	4.78 (4.43, 8.09)	
CL/F (L/hr/kg)	Mean (SD)	2.20 (2.03)	0.14 (0.01)	NC
	Median (min, max)	1.85 (0.40, 6.62)	0.14 (0.13, 0.15)	

Reviewers Comment:

- Mean active moiety PK parameters for the 4 mg once-daily dose were very similar to those reported in a previous trial conducted in 11 to 15-year-old patients with overactive bladder and in healthy adult volunteers, as seen in the following table.

Comparison of Active Moiety AUC_{0-24} and C_{max} in Adolescent (11 to 15 years old) and Adult Subjects after a 4 mg/day dose of Tolterodine MR Capsules

Parameter	Statistic	11-15 year old Neurogenic Bladder* N=10	11-15 year old Overactive Bladder [12] N=20	Healthy Adult Subjects [20] N=17
AUC_{0-24}(nM*hr)	Mean (SD)	27.3 (10.5)	29.7 (11.1)	30.4 (13.7)
	Median (min, max)	25.5 (11.5, 43.4)	26.7 (14.4, 52.3)	26 (13, 52)
C_{max} (nM)	Mean (SD)	2.10 (0.93)	2.17 (0.95)	2.3 (1.0)
	Median (min, max)	1.89 (1.03, 3.86)	2.07 (0.93, 5.25)	2.70 (0.77, 3.70)

Pharmacodynamics

All patients had at least some urodynamic data at all dose periods,except the withdrawn patient; however, at a number of patient-dose periods, some measurements could not be determined or were missing. In particular, maximal cystometric capacity (i.e., intravesical volume at 40 cm

H_2O pressure) and bladder wall compliance at 0 to 40 cm H_2O pressure were often undetermined due to the patient developing discomfort before 40 cm H_20 pressure was reached. This resulted in termination of bladder filling before these measurements could be quantified.

In general, the small sample size and considerable inter-patient variability are reflected in the wide 95% confidence limits. For this age group (and/or dosage form), there was no consistent relationship between improvement from baseline in the pharmacodynamic variables and dose.

Volume to First Detrusor Contraction, Functional Bladder Capacity and Leak Point Pressure (N=11)

		Volume to first detrusor contraction of magnitude >10 cm H2O pressure (mL)	Functional bladder capacity (mL)	Leak point pressure (cm H2O)
Baseline	Mean (SD)	132.4 (76.7)	232.0 (62.7)	33.9 (15.1)
	Median (min-max)	113.0 (23.0 to 253.0)	224.0 (132.0 to 370.0)	34.0 (8.0 to 63.0)
	Not reported	0	0	2
Period 1: 2 mg/day	Mean (SD)	146.2 (98.5)	311.1 (87.6)	32.4 (13.5)
	Median (min-max)	141.5 (24.0 to 336.0)	344.0 (141.0 to 428.0)	28.0 (18.0 to 53.0)
	Not reported	1	0	4
Period 2: 4 mg/day	Mean (SD)	155.4 (115.2)	223.2 (78.6)	46.4 (18.1)
	Median (min-max)	166.5 (31.0 to 302.0)	247.0 (90.0 to 327.0)	47.0 (28.0 to 71.0)
	Not reported	3	2	6
Period 3: 6 mg/day	Mean (SD)	133.6 (93.9)	286.1 (107.7)	22.8 (11.6)
	Median (min-max)	119.5 (27.0 to 339.0)	264.0 (169.0 to 549.0)	28.0 (6.0 to 35.0)
	Not reported	3	1	6
Change from baseline to period 1	Mean (SD)	25.9 (107.6)	79.1 (90.8)	2.0 (19.8)
	Median (min-max)	4.0 (-143.0 to 257.0)	74.0 (-83.0 to 250.0)	-5.0 (-17.0 to 33.0)
	H-L (95% c.i.)*	15.0 (-47.0, 107.5)	79.8 (21.0, 146.5)	1.8 (-16.5, 26.5)
	Not reported	1	0	4
Change from baseline to period 2	Mean (SD)	35.0 (59.4)	-3.8 (71.8)	5.8 (14.2)
	Median (min-max)	23.0 (-56.0 to 134.0)	-10.0 (-108.0 to 95.0)	8.0 (-11.0 to 23.0)
	H-L (95% c.i.)*	30.5 (-23.0, 93.0)	-6.5 (-70.0, 59.5)	6.0 (-11.0, 23.0)
	Not reported	3	2	6
Change from baseline to period 3	Mean (SD)	18.9 (114.4)	59.4 (67.0)	-6.4 (19.1)
	Median (min-max)	16.5 (-130.0 to 226.0)	49.5 (-22.0 to 179.0)	-6.0 (-33.0 to 21.0)
	H-L (95% c.i.)*	18.5 (-71.0, 129.0)	59.5 (8.5, 116.0)	-6.0 (-33.0, 21.0)
	Not reported	3	1	6

Intravesical Volume (N=11)

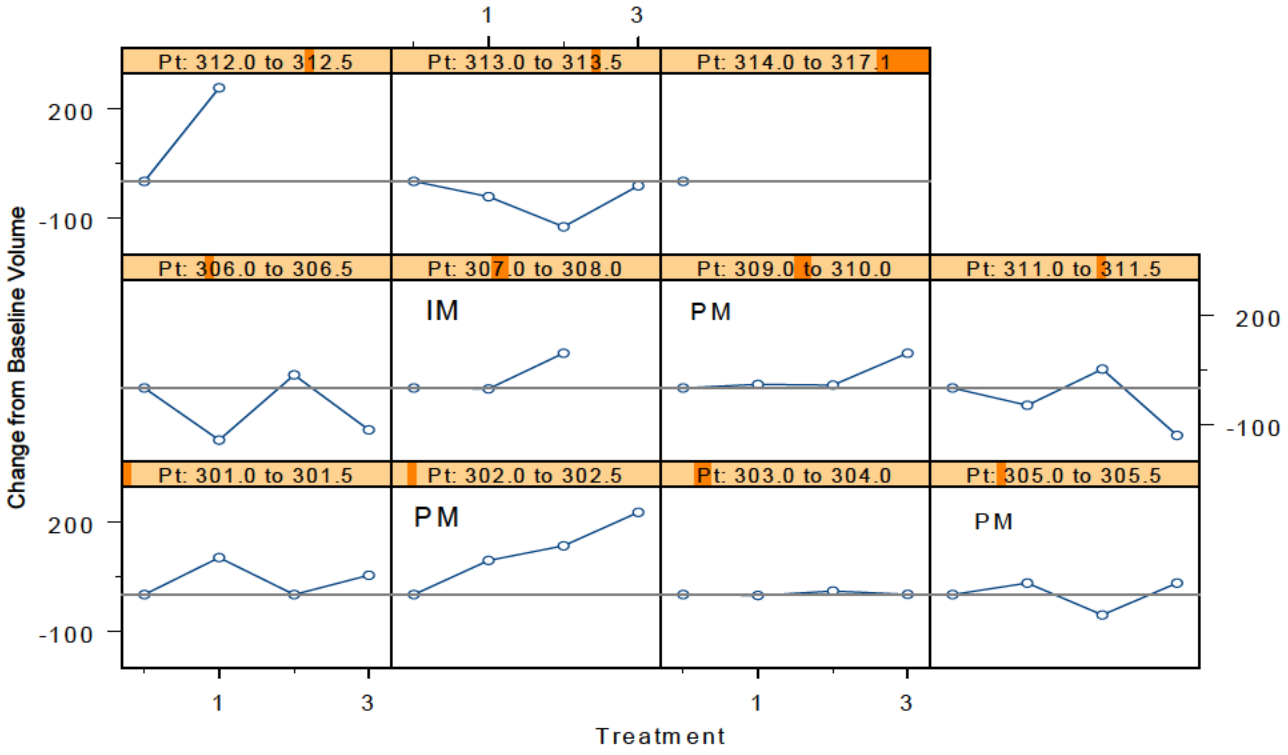
		Intravesical volume at 20 cm H2O pressure (mL)	Intravesical volume at 30 cm H2O pressure (mL)	Intravesical volume at 40 cm H2O pressure (mL)
Baseline	Mean (SD)	150.1 (95.4)	153.6 (47.6)	197.7 (49.0)
	Median (min-max)	132.0 (70.0 to 370.0)	167.0 (90.0 to 210.0)	206.0 (145.0 to 242.0)
	Not reported	2	6	8
Period 1: 2 mg/day	Mean (SD)	193.7 (101.2)	270.8 (109.3)	338.7 (102.7)
	Median (min-max)	180.0 (75.0 to 340.0)	295.5 (119.0 to 384.0)	360.0 (227.0 to 429.0)
	Not reported	2	5	8
Period 2: 4 mg/day	Mean (SD)	209.9 (87.4)	192.4 (92.3)	184.3 (99.2)
	Median (min-max)	217.5 (62.0 to 309.0)	176.0 (80.0 to 313.0)	164.0 (88.0 to 321.0)
	Not reported	3	6	7
Period 3: 6 mg/day	Mean (SD)	205.4 (120.3)	233.4 (68.9)	246.2 (69.4)
	Median (min-max)	183.5 (62.0 to 450.0)	225.0 (159.0 to 327.0)	217.0 (188.0 to 353.0)
	Not reported	3	4	6
Change from baseline to period 1	Mean (SD)	72.8 (104.2)	143.7 (102.9)	134.5 (74.2)
	Median (min-max)	69.5 (-94.0 to 229.0)	94.0 (75.0 to 262.0)	134.5 (82.0 to 187.0)
	H-L (95% c.i.)*	68.5 (-27.0, 170.5)	131.3 (., .)	134.5 (., .)
	Not reported	3	8	9
Change from baseline to period 2	Mean (SD)	56.0 (82.1)	22.8 (36.6)	-77.0 (28.3)
	Median (min-max)	55.0 (-72.0 to 164.0)	13.0 (-10.0 to 75.0)	-77.0 (-97.0 to -57.0)
	H-L (95% c.i.)*	56.8 (-40.0, 150.0)	15.0 (-10.0, 75.0)	-77.0 (., .)
	Not reported	4	7	9
Change from baseline to period 3	Mean (SD)	45.6 (67.9)	67.8 (61.7)	54.0 (111.7)
	Median (min-max)	36.0 (-58.0 to 128.0)	44.5 (23.0 to 159.0)	54.0 (-25.0 to 133.0)
	H-L (95% c.i.)*	42.5 (-37.5, 121.5)	45.3 (23.0, 159.0)	54.0 (., .)
	Not reported	4	7	9

Bladder Wall Compliance (N=11)

		Bladder wall compliance 0-20 cm H2O pressure (mL/cm H2O)	Bladder wall compliance 0-30 cm H2O pressure (mL/cm H2O)	Bladder wall compliance 0-40 cm H2O pressure (mL/cm H2O)
Baseline	Mean (SD)	7.5 (4.8)	5.1 (1.6)	4.9 (1.2)
	Median (min-max)	6.6 (3.5 to 18.5)	5.6 (3.0 to 7.0)	5.2 (3.6 to 6.1)
	Not reported	2	6	8
Period 1: 2 mg/day	Mean (SD)	9.7 (5.1)	9.0 (3.6)	8.5 (2.6)
	Median (min-max)	9.0 (3.8 to 17.0)	9.9 (4.0 to 12.8)	9.0 (5.7 to 10.7)
	Not reported	2	5	8
Period 2: 4 mg/day	Mean (SD)	10.5 (4.4)	6.4 (3.1)	4.6 (2.5)
	Median (min-max)	10.9 (3.1 to 15.5)	5.9 (2.7 to 10.4)	4.1 (2.2 to 8.0)
	Not reported	3	6	7
Period 3: 6 mg/day	Mean (SD)	10.3 (6.0)	7.8 (2.3)	6.2 (1.7)
	Median (min-max)	9.2 (3.1 to 22.5)	7.5 (5.3 to 10.9)	5.4 (4.7 to 8.8)
	Not reported	3	4	6
Change from baseline to period 1	Mean (SD)	3.6 (5.2)	4.8 (3.4)	3.4 (1.9)
	Median (min-max)	3.5 (-4.7 to 11.5)	3.1 (2.5 to 8.7)	3.4 (2.1 to 4.7)
	H-L (95% c.i.)*	3.4 (-1.4, 8.5)	4.4 (., .)	3.4 (., .)
	Not reported	3	8	9
Change from baseline to period 2	Mean (SD)	2.8 (4.1)	0.8 (1.2)	-1.9 (0.7)
	Median (min-max)	2.8 (-3.6 to 8.2)	0.4 (-0.3 to 2.5)	-1.9 (-2.4 to -1.4)
	H-L (95% c.i.)*	2.8 (-2.0, 7.5)	0.5 (-0.3, 2.5)	-1.9 (., .)
	Not reported	4	7	9
Change from baseline to period 3	Mean (SD)	2.3 (3.4)	2.3 (2.1)	1.4 (2.8)
	Median (min-max)	1.8 (-2.9 to 6.4)	1.5 (0.8 to 5.3)	1.4 (-0.6 to 3.3)
	H-L (95% c.i.)*	2.1 (-1.9, 6.1)	1.5 (0.8, 5.3)	1.4 (., .)
	Not reported	4	7	9

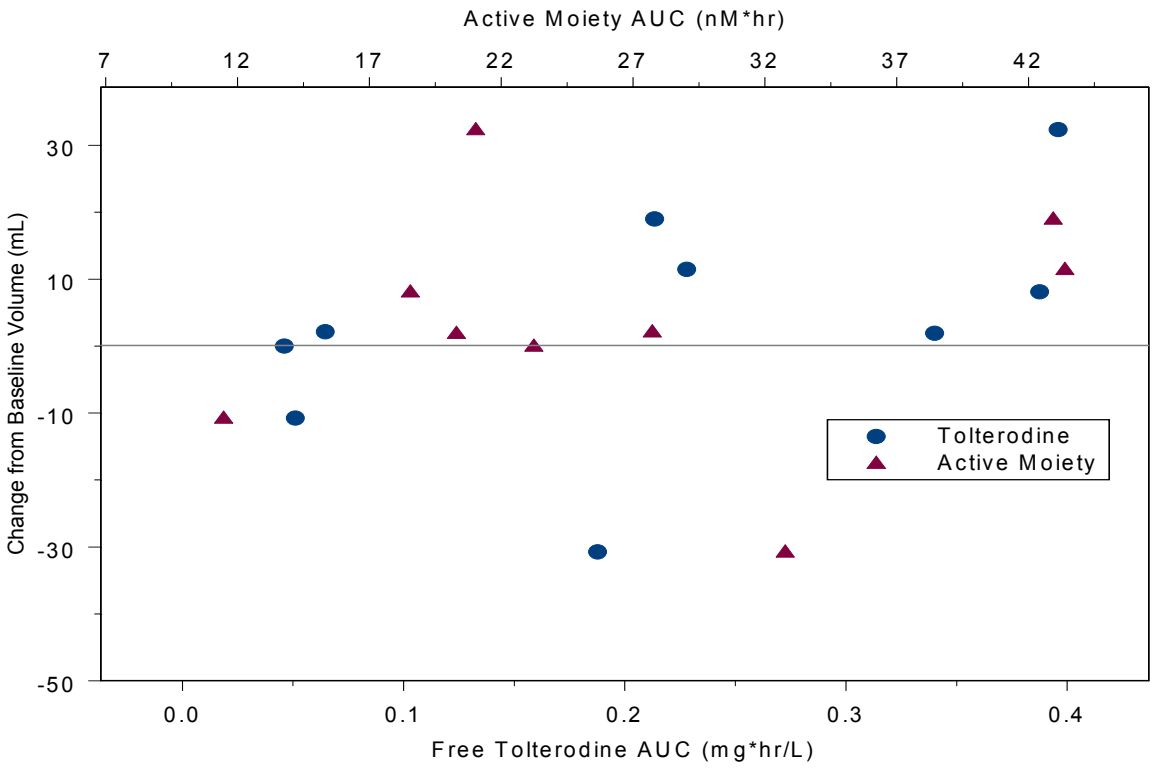
As in studies 001 and 002, individual data will be examined to validate the mean results presented by the sponsor.

Change from Baseline in Volume to First Detrusor Contraction (N=11)

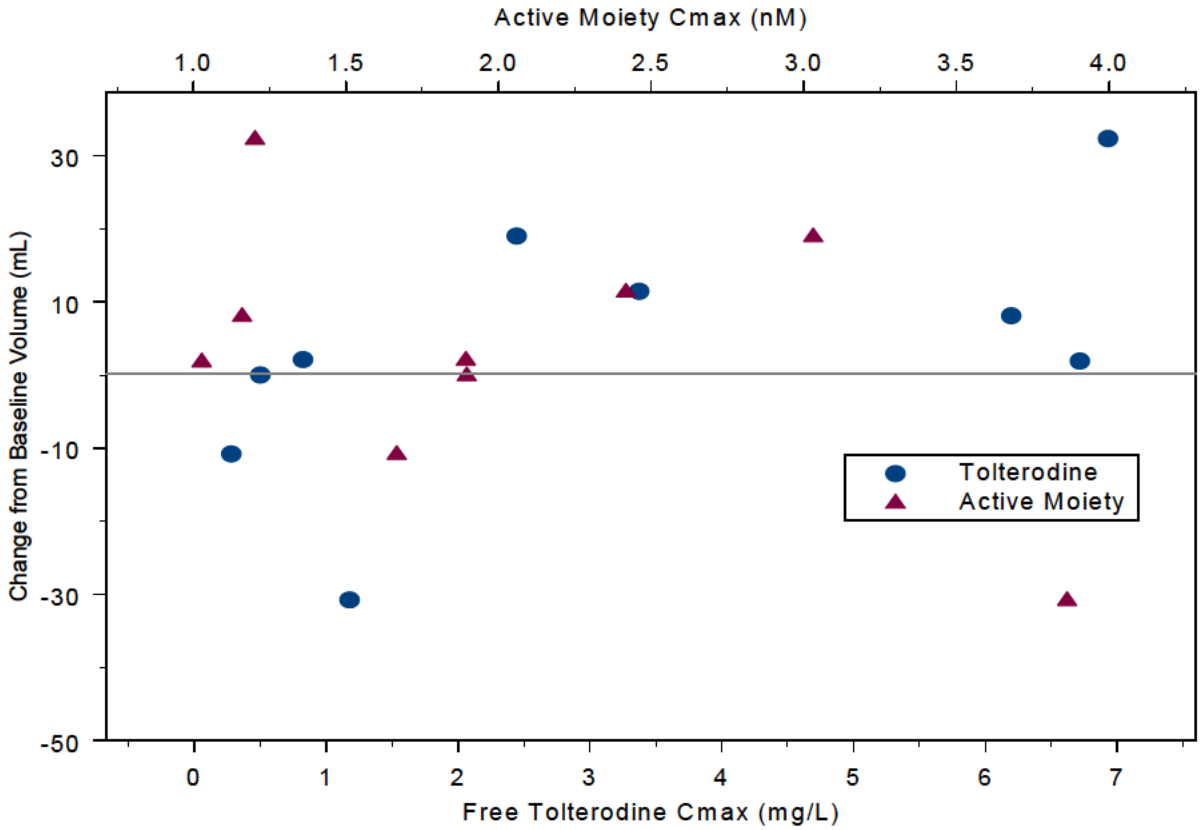


PM = Poor metabolizer
IM = Intermediate metabolizer
?? = not genotyped

Change from Baseline in Volume to First Detrusor Contraction vs. AUC of Free Tolterodine and Active Moiety (N=10)



Change from Baseline in Volume to First Detrusor Contraction vs. Cmax of Free Tolterodine and Active Moiety (N=10)



Reviewers Comments:

- Functional bladder capacity showed similar large mean increases from baseline at dose period 1 (+79.1 [± 90.8] mL) and dose period 3 (+59.4 [± 67.0] mL), but no change at dose period 2 (-3.8[± 71.8] mL).
- The volume to first detrusor contraction >10 cm H2O pressure showed mean increases from baseline for each dose period, but the increases were not dose related.
- Parallel improvements in micturition diary assessments were also observed. Non-dose-related decreases in the mean number of incontinence episodes/24 hours were seen. Small increases in mean volume per catheterization/micturition were also noted.
- In general, the small sample size and considerable inter-patient variability are reflected in the wide 95% confidence limits. There was no consistent relationship between improvement from baseline in the variables and dose. Additionally, no apparent relationships between the AUC of the active moiety and urodynamic or clinical response were observed at the 4 mg/day dose.
- Further analysis of the individual volume to first detrusor contraction data shows a lack of a dose-response relationship.
- **Based on all 3 Phase II studies, tolterodine (both MR and IR) shows little efficacy in these age groups at the doses studied. The medical officer suggested that it is not uncommon to need to treat the pediatric population with doses that lead to considerably higher exposures as compared to adults.**

C. General Biopharmaceutics

Two relative bioavailability studies were performed and submitted for review.

(i) Study 004 was an open, randomized, 3-way, single-dose, crossover, pharmacokinetic study in healthy volunteers (N=24). The primary objective of this study was to determine the relative bioavailability of two different tolterodine oral solutions compared to tolterodine IR tablets. Secondary objectives included comparing pharmacokinetic parameters for tolterodine, DD 01 and the active moiety after administration of two different tolterodine oral solutions relative to after IR tablets.

The primary endpoints are the $AUC_{0\text{-}inf}$ and C_{max} ratios for tolterodine and DD 01, respectively, after single-dose administration of each tolterodine liquid formulation relative to tolterodine IR tablets. The secondary endpoints included the $AUC_{0\text{-}inf}$ and C_{max} ratios for the active moiety after single-dose administration of each tolterodine liquid formulation relative to tolterodine IR tablets, the pharmacokinetic parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t(last)}$, C_{max}, t_{max} and $t_{1/2,z}$ for tolterodine and DD 01, respectively and V_z/F and CL/F for tolterodine.

The overall study design plan is as follows:

Study population: Healthy volunteers of CYP2D6 EM genotype
Number of subjects: 24
Study design: An open, randomized, 3-way, single-dose crossover, pharmacokinetic study

Treatments: 20 mL of two different tolterodine liquid formulations (one intended for commercial use, treatment A, and one prototype, treatment B) and two 2-mg immediate-release (IR) tablets of tolterodine (treatment C) were administered in a randomized order.

Treatment groups: Subjects randomly assigned to 6 treatment groups

Treatment sequence: 1: A, B, C
2: A, C, B
3: B, A, C
4: B, C, A
5: C, B, A
6: C, A, B

Study period duration: 1 day
Washout period: Minimum 7 days.
Duration of study: Approximately 38 days
Safety monitoring: AE monitoring and clinical lab tests

The following table lists the demographics of the subjects at screening.

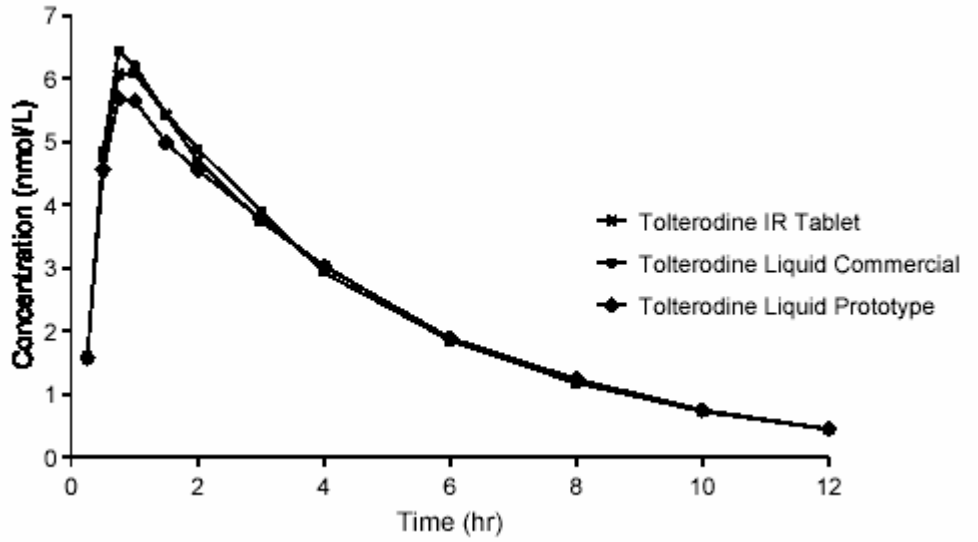
Demographic Characteristics at Screening. All Subjects.

		All Randomized Subjects, N=24
Sex	Male , n (%)	12 (50.0)
	Female, n (%)	12 (50.0)
Age (years)	Mean (SD)	26.6 (6.9)
	Median (min-max)	24.8 (19.2 to 47.1)
Race	Caucasian , n (%)	24 (100.0)
Weight (kg)	Mean (SD)	70.9 (11.8)
	Median (min-max)	68.0 (53.7 to 94.0)
Height (cm)	Mean (SD)	175.2 (8.5)
	Median (min-max)	172.9 (163.5 to 190.0)
BMI (kg/m2)	Mean (SD)	23.0 (2.4)
	Median (min-max)	22.6 (19.8 to 27.7)

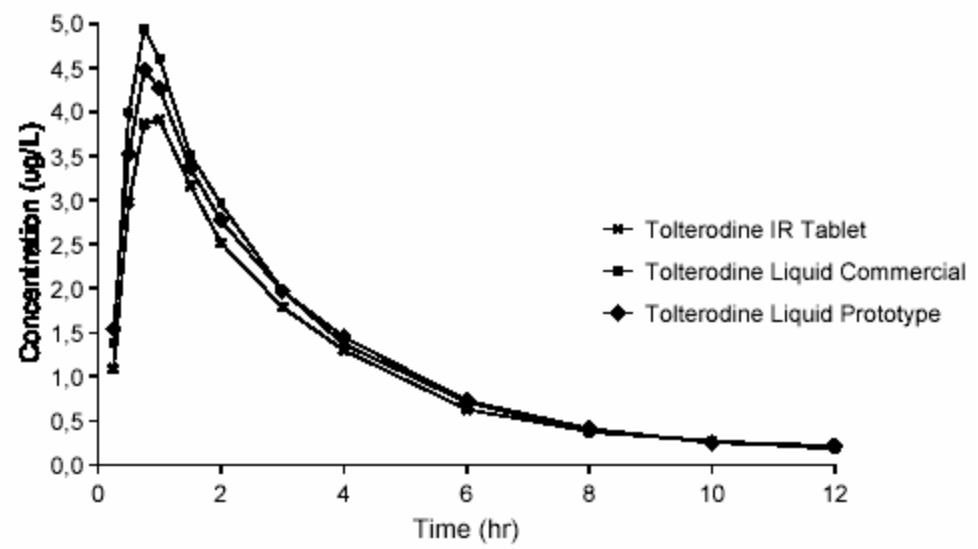
Age is years between date of birth and date of screening.
Body Mass Index is weight in kg / (height in m)2
Percentage (%) of total no. of subjects within the population.

The following figures show the mean concentrations of the active moiety, tolterodine and DD01.

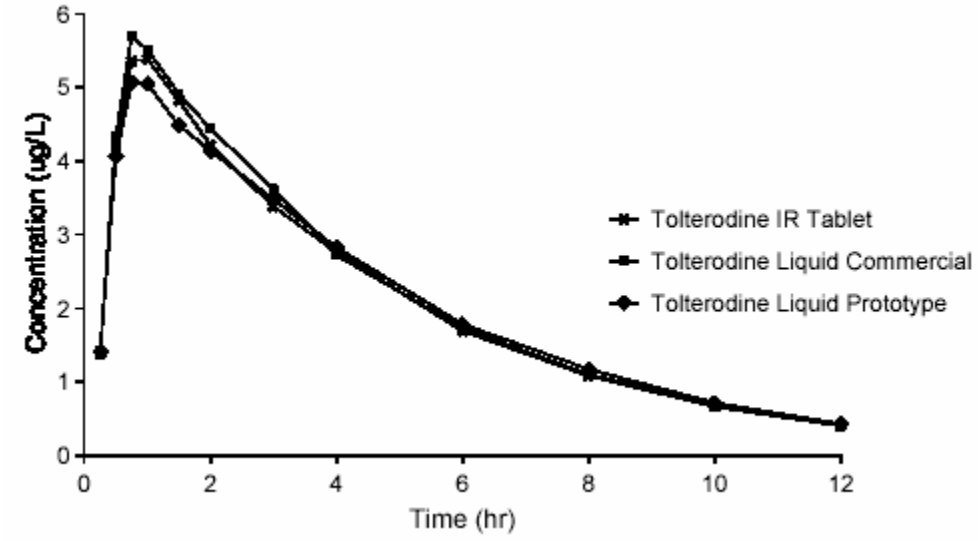
Mean Free Serum Concentration vs. Time Profile of the Active moiety



Total Serum Concentration vs. Time Profile of Tolterodine



Total Serum Concentration vs. Time Profile of DD01



The relative bioavailability, $AUC_{0\text{-}inf}$ ratio and C_{max} ratio with 90% confidence intervals are compiled in the following tables.

$AUC_{0\text{-}inf}$ Ratios

		Liquid Commercial vs IR Tablet N=24	Liquid Prototype vs IR Tablet N=24
Active moiety	Geometric Mean	1.047	1.017
	90% Confidence Interval	(1.003, 1.094)	(0.974, 1.062)
Tolterodine	Geometric Mean	1.231	1.191
	90% Confidence Interval	(1.081, 1.402)	(1.046, 1.356)
DD01	Geometric Mean	1.068	1.043
	90% Confidence Interval	(1.002, 1.137)	(0.980, 1.111)

C_{max} Ratios

		Liquid Commercial vs IR Tablet N=24	Liquid Prototype vs IR Tablet N=24
Active moiety	Geometric Mean	1.075	0.961
	90% Confidence Interval	(0.982, 1.177)	(0.878, 1.052)
Tolterodine	Geometric Mean	1.306	1.163
	90% Confidence Interval	(1.097, 1.553)	(0.978, 1.384)
DD01	Geometric Mean	1.089	0.984
	90% Confidence Interval	(0.986, 1.204)	(0.890, 1.087)

Reviewers Comments:

- **Bioequivalence criteria was not met for the parent, tolterodine.** With respect to the tolterodine data, neither liquid preparation was bioequivalent to the IR tablets. The commercial liquid and prototype liquid had a 23% (90% CI: 1.081, 1.402) and 19% (90% CI: 1.046, 1.356) higher $AUC_{0\text{-}inf}$, respectively, than the IR tablets. Additionally, the commercial liquid and prototype liquid had a 30% (90% CI: 1.097, 1.553) and 16% (90% CI: 0.978, 1.384) higher C_{max}, respectively, than the IR tablets.
- **Bioequivalence criteria was met for the active moiety and the active metabolite, DD01.**

The following tables list the PK variables for the active moiety, tolterodine and DD01.

PK Variables for the Active Moiety

		A Liquid Commercial N=24	B Liquid Prototype N=24	C IR Tablet N=24
$AUC_{0-\infty}$	Mean (SD)	30.9 (7.67)	30.2 (8.27)	29.9 (8.49)
(nM • hr)	Median (min-max)	29.5 (18.6 - 48.8)	29.1 (18.2 - 49.8)	29.0 (14.0 - 50.4)
C_{max}	Mean (SD)	7.06 (2.46)	6.25 (1.88)	6.59 (2.20)
(nM)	Median (min-max)	6.84 (3.14 - 13.3)	6.00 (3.02 - 9.61)	6.38 (2.49 - 10.4)

PK Variables for Tolterodine

		A Liquid Commercial N=24	B Liquid Prototype N=24	C IR Tablet N=24
$AUC_{0-\infty}$	Mean (SD)	15.8 (10.1)	15.5 (10.3)	13.6 (9.81)
(hr* µg/L)	Median (min-max)	15.5 (5.63 - 53.9)	13.7 (5.59 - 53.2)	12.4 (2.57 - 51.7)
AUC_{0-t}	Mean (SD)	15.3 (9.65)	15.0 (9.89)	13.0 (9.18)
(hr* µg/L)	Median (min-max)	15.1 (5.23 – 51.0)	13.2 (5.24 - 50.7)	12.1 (1.94 - 47.5)
C_{max}	Mean (SD)	5.34 (3.55)	4.82 (3.05)	4.28 (2.57)
(µg/L)	Median (min-max)	5.12 (1.45 - 16.9)	3.84 (1.58 - 12.8)	4.11 (0.516 - 10.3)
t_{max}	Mean (SD)	0.844 (0.219)	1.02 (0.493)	0.929 (0.342)
(hr)	Median (min-max)	0.750 (0.500 - 1.50)	1.00 (0.750 - 3.00)	0.875 (0.500 - 2.02)
λ_z	Mean (SD)	0.319 (0.064)	0.326 (0.048)	0.316 (0.059)
(1/hr)	Median (min-max)	0.311 (0.192 - 0.451)	0.332 (0.254 - 0.418)	0.320 (0.223 - 0.429)
$t_{1/2,z}$	Mean (SD)	2.26 (0.473)	2.17 (0.328)	2.27 (0.426)
(hr)	Median (min-max)	2.23 (1.54 - 3.61)	2.09 (1.66 - 2.73)	2.16 (1.62 - 3.10)
V_z/F	Mean (SD)	725 (348)	730 (360)	1031(927)
(L)	Median (min-max)	669 (216 - 1463)	656 (197 - 1433)	750 (238 – 3942)
CL/F	Mean (SD)	229 (117)	239 (124)	313 (254)
(L/hr)	Median (min-max)	177 (51.0 - 488)	201 (51.7 - 492)	221 (53.2 – 1070)

PK Variables for the Active Metabolite, DD01

		A Liquid Commercial N=24	B Liquid Prototype N=24	C IR Tablet N=24
$AUC_{0-\infty}$	Mean (SD)	28.5 (6.58)	27.9 (6.45)	27.0 (7.12)
(hr* µg/L)	Median (min-max)	27.4 (17.1 - 40.3)	27.7 (18.2 – 41.0)	25.9 (14.1 - 41.9)
AUC_{0-t}	Mean (SD)	26.4 (6.15)	26.0 (6.14)	25.1 (6.72)
(hr* µg/L)	Median (min-max)	26.2 (15.4 – 39.0)	25.6 (16.7 - 39.1)	24.2 (13.2 - 38.7)
C_{max}	Mean (SD)	6.30 (1.99)	5.62 (1.51)	5.82 (1.88)
(µg/L)	Median (min-max)	5.98 (2.82 - 11.5)	5.45 (3.31 - 8.77)	5.55 (2.49 - 10.0)
t_{max}	Mean (SD)	0.985 (0.479)	1.00 (0.590)	0.950 (0.417)
(hr)	Median (min-max)	1.00 (0.500 - 3.05)	0.750 (0.500 - 3.00)	0.750 (0.500 - 2.02)
λ_z	Mean (SD)	0.235 (0.041)	0.249 (0.047)	0.243 (0.038)
(1/hr)	Median (min-max)	0.231 (0.176 - 0.311)	0.239 (0.186 - 0.349)	0.236 (0.172 - 0.304)
$t_{1/2,z}$	Mean (SD)	3.03 (0.523)	2.88 (0.507)	2.92 (0.463)
(hr)	Median (min-max)	3.01 (2.23 - 3.93)	2.90 (1.99 - 3.72)	2.93 (2.28 - 4.03)

(ii) Study 005 was an open, randomized, 2-way, single-dose, crossover, pharmacokinetic study in healthy volunteers (N=30). The primary objective of this study was to compare the bioavailability of the beads from opened capsules sprinkled over applesauce to the intact tolterodine prolonged release capsules. Secondary objectives included assessing the PK parameters for the beads from the opened capsule.

The primary endpoints are the AUC_{0-inf} and C_{max} ratios for the active moiety of the beads from opened capsules sprinkled over applesauce relative to the intact tolterodine MR capsules. Secondary endpoints include the AUC0-∞ and Cmax ratios of tolterodine and DD 01 after the beads from opened capsules were sprinkled over applesauce relative to the intact tolterodine prolonged release capsules and the pharmacokinetic parameters AUC_{0-inf}, $AUC_{0-t(last)}$, C_{max}, t_{max} and $t_{1/2,z}$ for tolterodine and DD 01, respectively and V_z/F and CL/F for tolterodine.

The overall study design plan is as follows:

Study population: Healthy volunteers of CYP2D6 EM genotype
Number of subjects: 30
Study design: An open, randomized, 2-way, single-dose crossover, pharmacokinetic study

Treatments: A: Two 4-mg tolterodine prolonged release capsules were administered opened, the beads spread over applesauce.
B: Two 4-mg tolterodine prolonged release capsules were administered intact.

Treatment groups: Subjects randomly assigned to 2 treatment groups
Treatment sequence: Group 1: A B
Group 2: B A

Study period duration: 1 day
Washout period: Minimum 7 days.
Duration of study: Approximately 33 days
Safety monitoring: AE monitoring and clinical lab tests

The following table lists the demographics of the subjects at screening.

Demographic Characteristics at Screening. All Subjects.

		All Randomized subjects N=30
Sex	Male , n (%)	21 (70.0)
	Female, n (%)	9 (30.0)
Age (years)	Mean (SD)	26.2 (6.0)
	Median (min-max)	24.4 (19.4 - 42.8)
Weight, kg	Mean (SD)	73.6 (11.8)
	Median (min-max)	73.5 (55 - 96)
Height, cm	Mean (SD)	177 (10.4)
	Median (min-max)	178 (156 - 204)
BMI, kg/m²	Mean (SD)	23.4 (2.1)
	Median (min-max)	23.3 (19.6 - 28.7)
Race	White , n (%)	28 (93.3)
	Black , n (%)	1 (3.3)
	Mixed/Multiracial , n (%)	1 (3.3)
Genotype	Homozygous Extensive Metabolizers , n (%)	23 (76.7)
	Heterozygous Extensive Metabolizers, n (%)	7 (23.3)

The relative bioavailability, $AUC_{0\text{-}inf}$ ratio and C_{max} ratio with 90% confidence intervals are compiled in the following tables.

Relative bioavailability for tolterodine, DD01 and the active moiety based on the $AUC_{0\text{-}inf}$ ratio for the beads from the opened tolterodine prolonged release capsule relative to the intact capsule.

Substance		Tolterodine beads vs. intact capsule
Tolterodine	Geometric Mean	1.00
	90% Confidence Interval	(0.91, 1.09)
DD01	Geometric Mean	1.01
	90% Confidence Interval	(0.97, 1.06)
Active moiety	Geometric Mean	1.08
	90% Confidence Interval	(1.03, 1.14)

Relative bioavailability for tolterodine, DD01 and the active moiety based on the C_{max} ratio for the beads from the opened tolterodine prolonged release capsule relative to the intact capsule.

Substance		Tolterodine beads vs. intact capsule
Tolterodine	Geometric Mean	1.21
	90% Confidence Interval	(1.07, 1.37)
DD01	Geometric Mean	1.23
	90% Confidence Interval	(1.12, 1.35)
Active moiety	Geometric Mean	1.31
	90% Confidence Interval	(1.21, 1.43)

Reviewers Comments:

- **Bioequivalence criteria was not met for tolterodine, DD01 or the active moiety.** C_{max} for the beads opened over applesauce were 21% (90% CI:1.07, 1.37), 23% (90% CI: 1.12, 1.35) and 31% (90% CI: 1.21, 1.43) higher for tolterodine, DD01 and the active moiety relative to the intact capsule. However, $AUC_{0\text{-}inf}$ comparisons were equivalent for all analytes.

The following tables list the PK variables for the active moiety, tolterodine and DD01.

PK Variables for the Active Moiety

		Tolterodine beads N=30	Tolterodine intact capsule N=30
$AUC_{0-\infty}$ (nM·h)	Mean (SD)	48.35 (10.94)	45.09 (11.71)
	Median (min-max)	49.13 (25.29 - 70.84)	45.32 (22.58 - 68.50)
C_{max} (nM)	Mean (SD)	3.22 (1.29)	2.44 (0.93)
	Median (min-max)	3.11 (1.55 - 7.61)	2.38 (1.21 - 5.32)

PK Variables for Tolterodine

		Tolterodine beads N=30	Tolterodine intact capsule N=30
$AUC_{0-\infty}$ (µg/L·h)	Mean (SD)	33.81 (20.39)	32.91 (17.47)
	Median (min-max)	27.73 (8.07 - 104.31)	29.47 (10.87 - 85.36)
$AUC_{0\text{-}t(last)}$ (µg/L·h)	Mean (SD)	31.05 (19.52)	29.79 (17.07)
	Median (min-max)	26.38 (5.14 - 98.27)	26.58 (4.10 - 82.58)
C_{max} (µg/L)	Mean (SD)	2.79 (1.70)	2.26 (1.48)
	Median (min-max)	2.20 (0.41 - 6.04)	1.73 (0.35 - 6.68)
t_{max} (h)	Mean (SD)	4.51 (1.17)	4.83 (1.09)
	Median (min-max)	5.00 (2.00 - 7.00)	5.00 (2.00 - 8.00)
$t_{1/2,z}$ (h)	Mean (SD)	9.30 (6.51)	8.80 (10.29)
	Median (min-max)	7.46 (3.91 - 37.46)	6.35 (3.35 - 61.26)
V_z/F (L)	Mean (SD)	3534 (5057)	3140 (5855)
	Median (min-max)	1931 (447 - 27318)	2057 (373 - 33362)
CL_{PO} (L/h)	Mean (SD)	223 (139)	214 (108)
	Median (min-max)	198(53- 679)	186 (64 - 504)

PK Variables for the Active Metabolite, DD01

		Tolterodine beads N=30	Tolterodine intact capsule N=30
$AUC_{0-\infty}$ (µg/L·h)	Mean (SD)	48.31 (14.36)	47.73 (14.18)
	Median (min-max)	48.31 (16.33 - 80.64)	47.19 (17.19 - 72.06)
$AUC_{0-t(last)}$ (µg/L·h)	Mean (SD)	44.22 (13.40)	42.61 (12.75)
	Median (min-max)	43.97 (15.56 - 66.95)	43.55 (15.80 - 67.32)
C_{max} (µg/L)	Mean (SD)	3.30 (1.34)	2.69 (1.10)
	Median (min-max)	3.29 (1.33 - 7.41)	2.58 (1.08 - 5.92)
t_{max} (h)	Mean (SD)	4.74 (0.83)	5.57 (1.65)
	Median (min-max)	5.00 (3.00 - 6.00)	5.00 (3.00 - 12.00)
$t_{1/2,z}$ (h)	Mean (SD)	8.15 (3.29)	8.13 (4.02)
	Median (min-max)	7.27 (4.19 - 16.29)	7.22 (3.92 - 26.48)

4 Labeling Recommendations

As of 4/9/04, the label was mutually agreed upon between the sponsor and the agency.

5 Appendices

A. Pharmacometrics Review

Two separate pharmacometric analyses were performed. The first analysis involved pooling rich data from two pediatric phase I/II studies (Study 018 and 044). The second analysis involved using this model and incorporating sparse data from the two Phase III trials (008 and 020).

Introduction

The symptoms of overactive bladder comprise frequency, urgency, and urge incontinence of either idiopathic or neurogenic origin. Bladder overactivity is presumably caused by uncontrolled detrusor contractions during the filling phase. Tolterodine (Detrol® /Detrusitol®, TTD) is approved for treatment of overactive bladder in adults. Pediatric patients are, so far, not included in the labeling text.

From pharmacological *in vitro* studies, tolterodine has been characterized as a potent muscarinic receptor antagonist. The pharmacokinetics and pharmacodynamics of tolterodine have been investigated in a number of studies in adults. Tolterodine is rapidly absorbed after an oral dose with the maximum concentration reached about 1-2 hours after administration. A high degree of absorption has been shown in studies where the urinary recovery of orally administered tolterodine-derived radioactivity biotransformation has been determined to be 77 ± 4% (mean ± SD) of dose. Tolterodine is highly and selectively biotransformed by cytochrome P450 (CYP) 2D6, a polymorphically distributed isoenzyme, to the pharmacologically active 5-hydroxymethyl metabolite (DD 01). This metabolite mainly stands for the effect in extensive metabolizers. CYP2D6 is absent in approximately 7% of the Caucasian population as a result of mutations in the CYP2D6 gene. Individuals with deficient metabolism of a certain drug are called "poor metabolizers" and belong to the "PM-phenotype" as compared to the extensive metabolizers or

"EM-phenotype." The elimination half-life of tolterodine has been estimated to be 2-3 hours in extensive metabolizers and to be about 10 hours in poor metabolizers. The accumulation of tolterodine and DD 01 in serum is low after doses of 2 and 4 mg b.i.d.

This analysis details the development of a population pharmacokinetic model describing the pharmacokinetics of tolterodine in two distinct populations of children: those aged 5-10 years given the immediate-release (IR) formulation (Study 044) and those aged 11-15 years given the prolonged-release (MR) formulation (Study 018).

Reviewers comment:

- Due to the design of the studies pooled for this analysis, there is no way to distinguish the effect of formulation from the effect of age.

Objectives

- To develop a population pharmacokinetic model which describes the pharmacokinetic disposition of the immediate-release formulation in children 5 to 10 years of age and the prolonged-release formulation in children 11 to 15 years of age;
- To evaluate the influence of patient covariates on the pharmacokinetic parameters of tolterodine; and
- To facilitate the Bayesian predictions of drug exposure for safety and efficacy evaluation in future clinical trials.

Methodology

Study 018 Protocol

This was a Phase I, open-label, dose-escalation pharmacokinetic study of tolterodine in patients aged 11 to 15 years. Subjects were eligible for this study if they were within the normal height and weight ranges and had urinary urgency and frequency (on average of ≥ 8 micturitions per 24-hour period) and/or urge incontinence with at least one incontinence episode per week. Each subject received an oral dose of either 2 or 4 mg tolterodine q.d. in the prolonged-release formulation. Up to eleven blood samples for determination of tolterodine and DD 01 were collected pre-dose (maximum 10 minutes before) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, and 25 hours post-dose on the PK visit day (Day 7 or 8, at steady state). The duration of treatment was 7-10 days.

Study 044 Protocol

This was an open, uncontrolled safety and pharmacokinetic study of tolterodine in subjects aged 5 to 10 years. Subjects were eligible for this study if they were within the normal height and weight ranges and had urinary urgency and frequency (on average of ≥ 8micturitions per 24-hour period) and/or urge incontinence with at least one incontinence episode per week. Each subject received an oral dose of 0.5, 1, or 2 mg tolterodine b.i.d. in the immediate-release formulation. Venous blood samples for determination of tolterodine and DD 01 were collected prior to and at 0.5, 1, 2, and 3 hours post the first tolterodine dose on Day 1 and prior to and at 0.5, 1, 2, 3, 4, 6, and 8 hours post the last tolterodine dose on Day 14 (steady-state).

Study 008 Protocol

Study 008 was a double-blind, randomized, placebo-controlled, multinational, and multicenter study with two parallel groups. Each patient was randomized to receive either tolterodine prolonged release 2 mg, once daily, or placebo for 12 weeks in a ratio of 2:1. Sample size was determined to be approximately 300 patients (200 tolterodine, 100 placebo). The total expected duration of patient participation (Visits 1 through 4) was 13 to 14 weeks, divided as: 1-week washout (if required), 1-week run-in, followed by study treatment for 12 weeks.

Tolterodine prolonged release (MR) 2 mg capsules or placebo capsules were administered orally, once daily, in the morning, with water and preferably swallowed whole. Alternatively the capsules may have been emptied and the contents (beads) mixed into soft food. **Note that a BA/BE study (detailed earlier) showed that swallowing the capsule whole is not bioequivalent to opening the capsule over applesauce and ingesting.** However, the beads were not crushed or chewed. The medication was taken with food or on an empty stomach. It was assumed that the method of administration did not influence the pharmacokinetics of the drug.

Study 020 Protocol
Study 020 was a double-blind, randomized, placebo-controlled, multinational, and multicenter study with two parallel groups. Each patient was randomized to receive either tolterodine prolonged release 2 mg, once daily, or placebo for 12 weeks in a ratio of 2:1. Sample size was determined to be approximately 300 patients (200 tolterodine, 100 placebo). The total expected duration of patient participation (Visits 1 through 4) was 13 to 14 weeks, divided as: 1-week washout (if required), 1-week run-in, followed by study treatment for 12 weeks. The dosing regimen and method/timing of drug administration were the same as in Study 008.

Patient Covariates
The following patient demographic and clinical biochemical factors were explored, where appropriate, for their predictive ability in reducing the between-subject variability in tolterodine pharmacokinetic parameters: age, weight, weight percentile, height, body surface area (BSA), gender, race, creatinine clearance, alpha-1 acid glycoprotein, hemoglobin, and drug formulation. Body surface area was evaluated using patient weight and height as measured at Visit 1 or baseline and assumed constant over the course of the trials. Weight percentile was calculated using the CDC percentile data as well as the methods for calculation described on their web site. BSA in m^2 was calculated using the method of Gehan and George as shown below:

$$BSA = 0.0235 * \text{Height (cm)}^{0.4222} * \text{Weight (kg)}^{0.515}$$

Creatinine clearance (CL_{CR}) was calculated using the Schwartz et al. method as shown below:

$$CLcr\ (mL/min) = K*\text{Body length (cm)}/S_{CR}(mg/dL)*BSA\ (m^2)/1.73$$

Where,

Body length (cm) = height in cm;
BSA = body surface area in m2;
Scr = Serum creatinine in mg/dL; and

K = a constant relating age and gender to urinary creatinine per unit of body size:

Age group	K
Low birth weight infants, ≤ 1 yr	0.33
Term infants, ≤ 1 yr	0.45
Children: 2-12 yrs	0.55
Children: 13-21 yrs	
Females	0.55
Males	0.70

The concentration-time data were initially explored graphically for evidence of one and two compartments, linearity and nonlinearity, and ability to combine data from different studies. This exploration was performed on both the pooled population concentration-time profiles and the individual concentration-time profiles. Various structural models were evaluated on the basis of the reasonability and precision of parameter estimates, the residual variability, the value of the objective function, and the goodness-of-fit. A proportional residual error model was used during this process unless significant bias was encountered in the fit of the models; if necessary, alternate residual error models were evaluated.

Model selection was based on the statistical significance of the change in the log likelihood value obtained for various models. For each analysis, NONMEM® computes the minimum value of the objective function, a statistical parameter that is proportional to minus twice the log likelihood of the data. In the case of hierarchical models, the change in the minimum value of the objective function produced by the inclusion or deletion of a parameter is asymptotically distributed as χ^2 with the number of degrees of freedom equal to the number of parameters added to or deleted from the model. In the case of non-hierarchical models, the minimum value of the objective function was only used as a qualitative measure of statistical significance in evaluating alternative models.

The goodness-of-fit of each NONMEM® analysis was also assessed by examination of the following:

- scatterplots of predicted serum concentrations versus measured serum concentrations and versus weighted residuals;
- the precision of the parameter estimates as measured by the percent standard error of the mean (%SEM = standard error / parameter estimate * 100); and
- changes in the estimates of interindividual and residual variability for the specific model.

Results

Drug formulation and patient age were different in Studies 018 and 044, therefore, the apparent absorption rate, apparent metabolic ratio, and apparent elimination rate could be quite different in patients from these two studies even though the overall metabolic pathways are still the same. Therefore, a step-by-step approach to the population PK analysis was used. As the first step of the approach, three separate datasets were created: Study 018 alone, Study 044 alone, and both studies combined. Separate structural models were developed to fit the datasets for Studies 018

and 044. Then, a structural model based on these two structural models was developed for the combined dataset.

Based on prior information about the pharmacokinetics and pharmacodynamics of tolterodine in adults, the pharmacokinetics are expected to be linear in the dose range used in this analysis. Therefore, the PK model construction was started using the linear models. Further, based on the prior information of the metabolic pathways of tolterodine in humans and the fact that only tolterodine and DD 01 are active, the model structure was simplified. That is, a three compartment model (one for drug depot, one for tolterodine, and one for DD 01) was used to best express the pharmacokinetics of tolterodine and DD 01. Other models, such as four-compartment models (one for drug depot, two for tolterodine, and one for DD 01), were also tested but did not provide a significantly better fit of the data than the three-compartment model. The model development was accomplished in three steps: structural model development, covariate/random effect evaluation, and model refinement/testing/validation. As the formulation administered and the age range of the patients was different in Studies 018 and 044, separate structural PK models were developed for each study. Subsequently, a comprehensive structural model was developed for the combined dataset. Covariate/random effect evaluation was performed on the comprehensive structural model for the combined dataset only.

Study 018

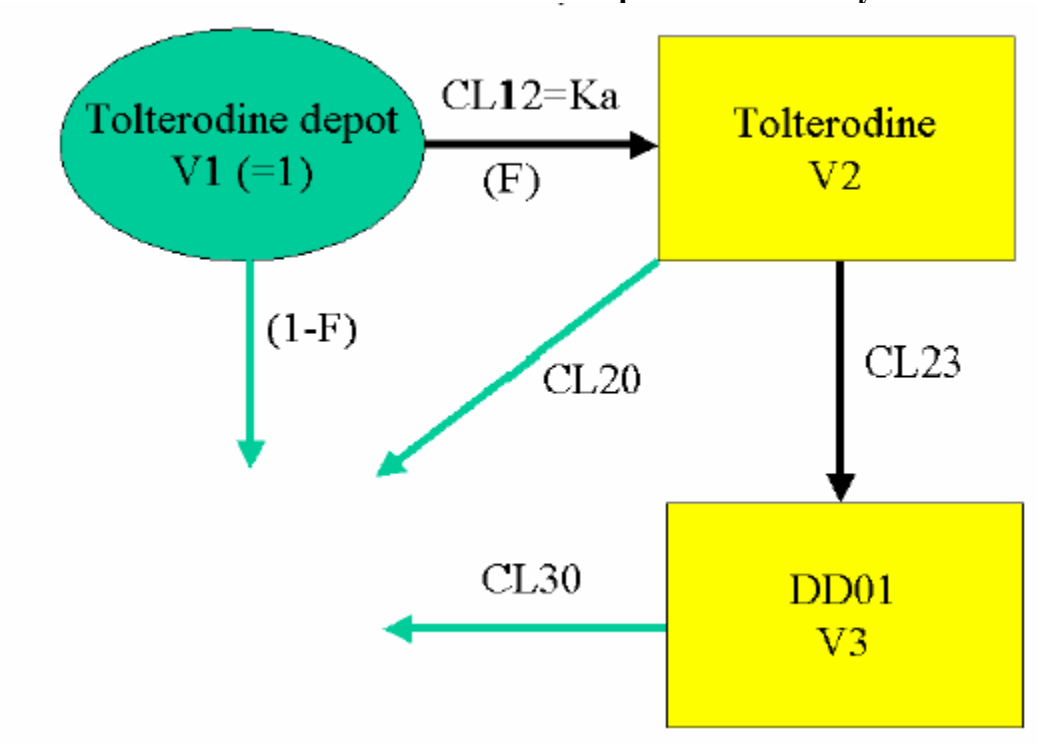
Summary statistics for the patient demographic and clinical biochemistry covariates evaluated in the development of the population pharmacokinetic model in children from Study 018 are listed in the following table.

Summary Statistics for the Patient Demographic Characteristics – Study 018

Variable	Abbreviation	n (%)	Mean (SD)	Minimum	Median	Maximum
Age (yrs)	AGE	30 (100)	12.9 (1.17)	10.9	13.0	14.7
Alpha-1 acid glycoprotein (mg/dL)	AGP	30 (100)	0.86 (0.14)	0.61	0.85	1.27
Height (cm)	HTCM	30 (100)	158 (9.9)	134.7	156.6	175.9
Weight (kg)	WTKG	30 (100)	62.2 (19.8)	30.4	61.4	125.3
Body Surface Area (m^2)	BSA	30 (100)	1.66 (0.30)	1.08	1.63	2.51
Creatinine clearance (mL/min)	CLCR	30 (100)	142.8 (37.2)	77.1	136.7	239.4
Gender						
Males	SEXM	12 (40)	----	----	----	----
Females	SEXF	18 (60)				
Ethnicity						
Caucasian	RACW	26 (86.7)	----	----	----	----
Black	RACB	4 (13.3)				
Phenotype						
Extensive Metabolizer	EM	28 (93.3)	----	----	----	----
Poor Metabolizer	PM	2 (6.7)				
CYP2D6 inhibitor	DEC2	4 (13.3)	----	----	----	----
CYP3A4 inhibitor	DEC3	2 (6.7)	----	----	----	----

A three-compartment model was successfully fit to the data. Addition of a peripheral compartment to the model for tolterodine PK slightly improved the fitting of the model to the tolterodine concentrations. However, the parameter estimates for the peripheral compartment were unusually large and unstable. This implies that data to support the estimation of parameters for the peripheral compartment are insufficient. On the other hand, addition of a lag time to the drug absorption process in the model was found to significantly improve the quality of fitting. The estimate of lag time was reasonable and stable. Therefore, the three-compartment model with a lag time for absorption was selected as the structural model for the data from Study 018. The PK parameter estimates for this model are listed in the following table.

Model Structure for Tolterodine Population PK Analysis



Parameter Estimates and Standard Errors for the Base Structural Model – Study 018

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
K_a, absorption of TTD (L/hr)	0.0469	12.8	42.6	49.9
CL20, TTD clearance through intact excretion and other metabolic pathways (L/hr)	22.9	15.0	149	21.3
Clearance ratio: CL23/CL30	2.10 FIXED	NA	NA	NA
CL23, TTD clearance through conversion to DD 01 (L/hr)	NA	NA	82.7	28.7
CL30, DD 01 clearance through intact excretion and other metabolic pathways (L/hr)	79.4	10.0	NE	NE
V2, Volume of distribution for TTD (L)	127	25.7	159	48.4
V3, Volume of distribution for DD 01 (L)	59.4	17.2	0 FIXED	NA
Lag time for TTD absorption (hr)	0.345	19.4	128	148.2
Residual variability of TTD (%CV)	32.4	25.7	-----	-----
Residual variability of DD 01 (%CV)	17.0	23.2	----	----

Minimum Value of the Objective Function = -285.915

Note: NA – Not applicable; NE – Not estimated

Study 044

Summary statistics for the patient demographics and clinical biochemistry covariates evaluated in the development of the population pharmacokinetic model in children from Study 044 are listed in the following table.

Summary Statistics for the Patient Demographic Characteristics – Study 044

Variable	Abbreviation	n (%)	Mean (SD)	Minimum	Median	Maximum
Age (yrs)	AGE	33 (100)	7.38 (1.38)	5.0	7.3	10.2
Alpha-1 acid glycoprotein (mg/dL)	AGP	32 (97)	0.84 (0.28)	0.4	0.8	1.5
Height (cm)	HTCM	33 (100)	125 (9.3)	110	124	147
Weight (kg)	WTKG	33 (100)	26.8 (5.82)	17	25	39
Body Surface Area (m^2)	BSA	33 (100)	0.98 (0.14)	0.73	0.94	1.26
Creatinine clearance (mL/min)	CLCR	33 (100)	80.2 (16.5)	47.4	75.0	113.3
Gender Males Females	 SEXM SEXF	 20 (60.6) 13 (39.4)	----	----	----	----
Ethnicity Caucasian Black Other	 RACW RACB RACO	 31 (93.9) 1 (3.03) 1 (3.03)	----	----	----	----
Phenotype Extensive Metabolizer Poor Metabolizer	 EM PM	 30 (90.9) 3 (9.1)	----	----	----	----
CYP2D6 inhibitor	DEC2	0 (0)	----	----	----	----
CYP3A4 inhibitor	DEC3	1 (3.0)	----	----	----	----

Similar to Study 018, a three-compartment model was successfully fit to the data. However, in Study 044, no obvious second phase could be found in the concentration-time profiles; data were insufficient to support a peripheral compartment to the model for tolterodine PK. In addition, no significant lag time could be identified, as expected for the immediate-release formulation. Therefore, the selected structural model for the clinical trial data from Study 044 was a three-compartment model. The PK parameter estimates for this model are listed in the following table.

Parameter Estimates and Standard Errors for the Base Structural Model – Study 044

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
K_a, absorption of TTD (L/hr)	0.214	5.5	0 FIXED	NA
CL20, TTD clearance through intact excretion and other metabolic pathways (L/hr)	10.3	15.3	144	33.8
Clearance ratio: CL23/CL30	2.10 FIXED	NA	NA	NA
CL23, TTD clearance through conversion to DD 01 (L/hr)	NA	NA	57.4	41.2
CL30, DD 01 clearance through intact excretion and other metabolic pathways (L/hr)	37.8	14.6	NE	NE
V2, Volume of distribution for TTD (L)	18.1	23.3	124	22.6
V3, Volume of distribution for DD 01 (L)	3.74	61.2	NE	NE
Lag time for TTD absorption (hr)	0 FIXED	NA	NA	NA
Residual variability of TTD (%CV)	38.5	27.7	-----	-----
Residual variability of DD 01 (%CV)	37.3	36.7	----	----

Minimum Value of the Objective Function = 426.407

Note: NA – Not applicable; NE – Not estimated

The estimated PK parameters as a function of covariates can be expressed as in the following equations.

$$K_a = 0.0473*(1+3.03*IR)*(1+0.615*(EM-0.92))*(AGE/10)^{-0.353}*(1-0.299*(RACC-0.905))e^{N(0,0.0983)} \quad \textbf{(4)}$$

$$CL_{TTD} = 17.9*(WTKG/43.7)^{0.975}*(1-0.627*(IR-0.52))*(1-0.858*DEC3)*e^{N(0,1.50)} \quad \textbf{(5)}$$

$$CL_{TTD->DD\,01} = 15.4*2.10*EM*\ (AGP/0.848)^{-1.60}*(HTCM/141)^{1.54}*(1+0.770*(RACC-0.905))*e^{N(0,0.624)} \quad \textbf{(6)}$$

$$CL_{DD\,01} = 67.8*(HTCM/141)^{2.05}*(AGP/0.848)^{-1.23}*(1-0.228*(IR-0.52))*(1+0.538*(RACC-0.905)) \quad \textbf{(7)}$$

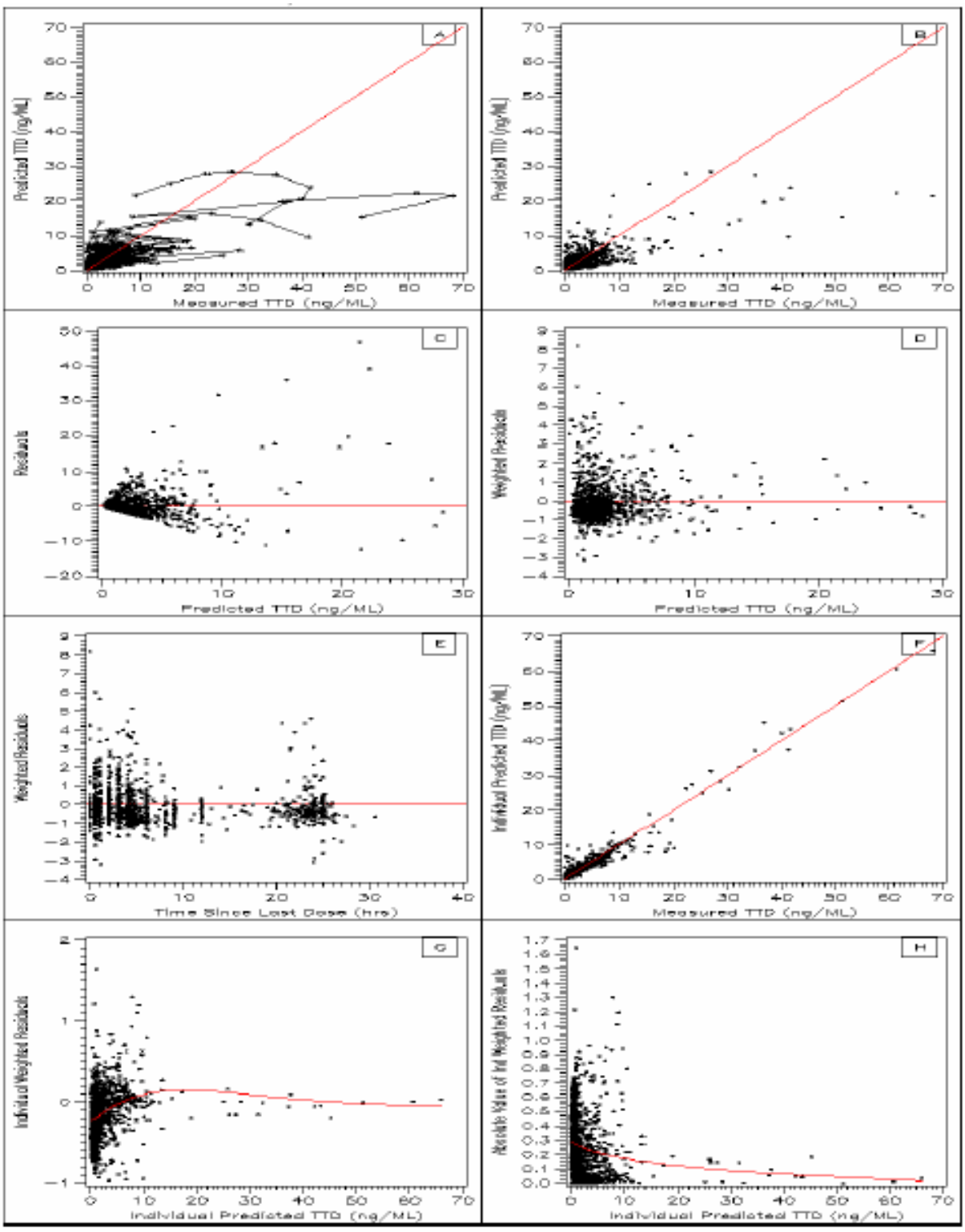
$$V_{TTD} = 46.7*(1-1.16*(IR-0.52))*(1+0.758*(AGEC-0.52))*(AGP/0.848)^{-1.61}*(1-1.28*(RACC-0.905))*e^{N(0,4.66)} \quad \textbf{(8)}$$

$$V_{DD\,01} = 25.5*(AGP/0.848)^{-1.53}*(BSA/1.30)^{1.67}*e^{N(0,1.79)} \quad \textbf{(9)}$$

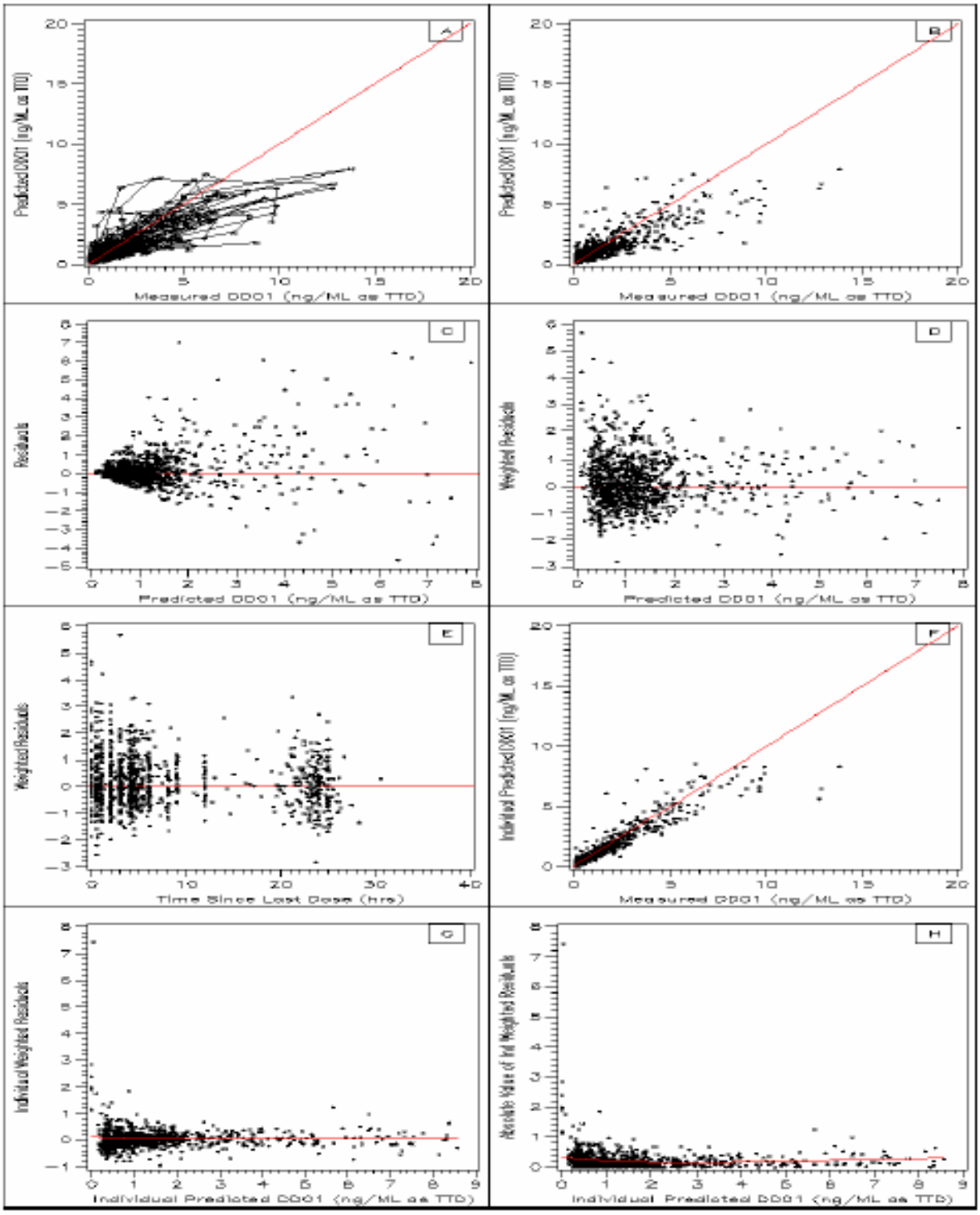
$$T_{lag} = 0.715*PR*e^{N(0,\,0.127)} \quad \textbf{(10)}$$

The goodness of fit can be seen in the following figures.

Goodness-of-Fit Graphs for the Tolterodine Concentrations using the Final, Refined Model – All Studies Combined



Goodness-of-Fit Graphs for the DD 01 Concentrations using the Final, Refined Model – All Studies Combined



Reviewers comments:

- The refined population pharmacokinetic model performed well in the prediction of the measured tolterodine and DD 01 concentrations and should provide accurate exposure estimates.

- In general, the administration of tolterodine MR 2 mg qd resulted in steady-state AUC_{0-24} values considerably lower than those seen in adults given tolterodine MR 4 mg QD. This was most apparent in patients with a body weight above 25 kg.
- Pharmacokinetic/pharmacodynamic analyses of the Study 008 data alone revealed a threshold exposure (AUC0-24) for response of approximately 14 nM*hr of the active moiety.
- Multivariable linear regression modeling analyses indicated that the two significant predictors of response, in terms of change from baseline in number of incontinence episodes per week at Week 12, were baseline incontinence episodes and whether or not the patient achieved the threshold exposure.
- Analyses of the combined data from Studies 008 and 020 supported the results from the Study 008 data analyses.
- Modification of the dosage regimen in children to allow heavier children to receive higher doses should result in the majority of patients attaining exposures above the threshold for response.

B. Filing Memo

1. Office of Clinical Pharmacology and Biopharmaceutics

2. *New Drug Application Filing and Review Form*

(1) General Information About the Submission

	Information		Information
NDA Number	**21,228/20,771**	**Brand Name**	**Detrol and Detrol LA**
OCPB Division (I, II, III)	**DPE II (HFD 870)**	**Generic Name**	**Tolterodine tartrate**
Medical Division	**DRUDP (HFD 580)**	**Drug Class**	**Antimuscarinic**
OCPB Reviewer	**Stephan R. Ortiz, R.Ph., Ph.D.**	**Indication(s)**	**Overactive bladder**
OCPB Team Leader	**Ameeta Parekh, Ph.D.**	**Dosage Form**	**IR, LA, liquid**
		Dosing Regimen	**Daily, BID**
Date of Submission	**10/10/2003**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**3/15/2004**	**Sponsor**	**Pfizer**
PDUFA Due Date	**4/16/2004**	**Priority Classification**	**3S (Ped. Exclusivity)**
Division Due Date	**3/16/2004**		

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.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary				
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**			
multiple dose:				
Patients-				
single dose:	**X**			
multiple dose:	**X**			
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:	**X**			
geriatrics:				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	**X**			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**			
Population Analyses -				
Data rich:				
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**2**		
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				
Total Number of Studies				
		10 (including POP-PK reports)		

Filability and QBR comments

	"X" if yes	
Application filable ?	**X**	
Comments sent to firm ?		
QBR questions (key issues to be considered)		

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

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

/s/

Stephan Ortiz
4/12/04 03:32:51 PM
BIOPHARMACEUTICS

Ameeta Parekh
4/12/04 03:37:26 PM
BIOPHARMACEUTICS
Concur