CLINICAL PHARMACOLOGY REVIEW

NDA:	20-579 / S-026
Type/Category:	505(b)(1)/SE8
Brand Name:	Flomax®
Generic Name:	Tamsulosin hydrochloride (HCl)
Relevant IND:	IND 30,365
Indication:	Treatment of pediatric patients 2 years - 16 years of age with elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida).
Dosage Form:	Capsules
Route of Administration:	Oral
Dosing Regimen and Strength:	Once daily, 0.4 mg
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Dates:	June 25, 2009 (efficacy supplement) September 30, 2009; October 1, 2009; October 2, 2009; and October 15, 2009 (additional information)
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1 EXECUTIVE SUMMARY

Tamsulosin hydrochloride (HCl) was developed as a modified-release (MR) capsule for the treatment of benign prostatic hyperplasia (BPH) in adults and was approved in the US for this indication under NDA 20-579 on April 15, 1997. Tamsulosin HCI is available as Flomax® 0.4 mg capsules.

This supplemental new drug application (sNDA) was submitted with clinical data (SE-8) to the Flomax® NDA 20-579 including a proposal to update labeling and is intended to support two objectives. The first is to provide complete information and appropriate proposed pediatric labeling in response to the written request (WR). The second objective is to take the opportunity and reformat the Flomax® package insert in order to establish compliance with the Physician's Label Rule (PLR) (21 CFR 201.57).

A formal WR was sent to Boehringer Ingelheim Pharmaceuticals, Inc. on January 10, 2006. The WR was regarding the assessment of pediatric indication for treatment of pediatric patients (2-16 years of age) with elevated detrusor leak point pressure (LPP) associated with a known neurological disorder (e.g., spina bifida) and the development of an age-appropriate formulation for the proposed pediatric indication.

The WR had three subsequent formal amendments outlining a specific and agreed upon development plan. It consists of two clinical trials, designated as Study 1 (Study 527.66) and Study 2 (Study 527.51), to characterize the PK, and evaluate the safety and efficacy of tamsulosin HCl for the proposed pediatric indication. The agreed upon timeframe for submitting reports from these studies to the Agency was on or before July 1, 2009. The Sponsor met the agreed timeline for submission and the studies were conducted according to the written agreement. As a result, the pediatric exclusivity board granted pediatric exclusivity to the Sponsor on September 17, 2009.

Upon completion and analysis of the results from the safety and efficacy trial, WR Study 2 (Study 527.51), it was determined by the Sponsor that efficacy in the targeted pediatric population could not be supported. Therefore, (b) (4)

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 20-579/SE8 submitted on June 25, 2009, October 1, 2009, October 2, 2009, and October 15, 2009. The overall Clinical Pharmacology information submitted to support this sNDA is acceptable.

1.2 POSTMARKETING REQUIREMENTS / COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Formulation for Pediatric Population

Tamsulosin HCl Capsules, 0.025 mg, 0.1 mg, and 0.2 mg were developed to provide an age-appropriate formulation for the pediatric population. The capsules were formulated for US pediatric

program as a (b) (4)

Dosing of the investigational pediatric capsules was accomplished by opening the capsules and sprinkling the contents over a teaspoon of applesauce or yogurt, followed by a spoonful of water. Information regarding the effect of mixing the granules with applesauce or other fruit sauces or yogurt on drug release was previously submitted to the Agency on April 4, 2006 (IND 30,356, SN 262) and September 25, 2006 (IND 30,365, SN 265). This was assessed by comparing the dissolution profiles of the tamsulosin HCl intact capsules, granules alone and granules in applesauce or other fruit sauces or yogurt. Dissolution data will be reviewed by the Office of New Drug Quality Assessment (ONDQA).

The development of the pediatric formulation included multi-national studies; therefore, it was necessary to use an alternate formulation of tamsulosin capsules in some participating countries. The alternate formulation is approved under the trademark of Omnic® in Europe and is identical to Flomax® with the exception of a small amount of the excipient, calcium stearate, which is used as (b) (4) The comparison of Flomax® and Omnic® formulations had been previously discussed with the Division during a January 12, 2005 Guidance meeting. The issue was noted in the final meeting minutes issued on February 9, 2005. The Division had accepted the Sponsor's strategy for establishment of equivalence between Flomax® and Omnic® on the basis of comparative dissolution data supported by high solubility and permeability data. Discussion on this topic is captured in the Type C Guidance held on November 24, 2008 (meeting minutes dated December 22, 2008 in DARRTS under IND 30,365). Equivalency was established by achieving multi-point dissolution similarity scores (f_2) of > 50 with results obtained for both products using three different dissolution media (per Dr. David Lewis' CMC review for NDA 20-579 / S-025 dated June 4, 2009 available in DARRTS).

In addition, a bioequivalence (BE) study (Study ARI10021, submitted under NDA 21-319/S-014, approved on June 19, 2008) comparing Omnic® 0.4 mg and Flomax® 0.4 mg under fasting condition showed that they are bioequivalent (information on this can be found in Dr. George Benson's Division Director/Cross Discipline Team Leader Review dated June 18, 2008 under NDA 21-319/S-014 available to public at:
http://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2008/021319se1-014_SUMR.pdf).

Pharmacokinetics of Tamsulosin in Pediatric Population

The PK of tamsulosin HCl in adults has been already well characterized. The two clinical trials in pediatric neurogenic population were conducted. Phase 2, Study 527.66 was conducted to characterize the PK/PD profile tamsulosin and Phase 2b/3, Study 527.51 was a dose ranging study with a sparse PK sampling to evaluate the safety and efficacy of different dose ranges (low, medium, high) of tamsulosin.

Study 527.66 (WR Study 1), an uncontrolled, open-label, titration study of tamsulosin HCl in children of either gender (ages 2-16 years) with neuropathic bladder, with a randomized PK sub-study investigating low, medium, and high weight-based (mg/kg) dose ranges, was conducted to characterize

the PK/PD profile and evaluate the long term safety (up to 12 months) and efficacy of tamsulosin HCl in children with an elevated detrusor LPP associated with a known neurological disorder (e.g., spina bifida). Tamsulosin HCl was given once daily 30 min after breakfast up to 12 months. A summary of the PK results from Study 527.66 is shown in Table 1.

Table 1: Summary of PK Parameters of tamsulosin after Single and Multiple Oral Administrations (Study 527.66)

	Single dose		Steady state					
	Low dose (0.001-0.002 mg/kg) (N=11)		Low dose (0.001-0.002 mg/kg) (N=10)		Medium dose (0.002-0.004 mg/kg) (N=9)		High dose (0.004-0.008 mg/kg) (N=10)	
	gMean	(gCV(%))	gMean	(gCV(%))	gMean	(gCV(%))	gMean	(gCV(%))
$C_{max,1}$ [ng/mL]	1.67	(68.8)	NA	NA	NA	NA	NA	NA
$C_{max,ss}$ [ng/mL]	NA	NA	2.79	(59.5)	5.02	(94.8)	14.1	(50.3)
$AUC_{\tau,ss}$ [ng·h/mL]	NA	NA	35.8	(75.6)	68.2	(94.7)	175	(61.0)
$t_{max,1}$* [h]	6.00	(2.00-8.00)	NA	NA	NA	NA	NA	NA
$t_{max,ss}$* [h]	NA	NA	5.00	(2.33-8.00)	5.92	(2.00-8.00)	5.01	(2.23-8.00)
$t_{1/2,ss}$ [h]	NA	NA	11.8	(48.1)	10.3	(40.8)	14.0	(31.9)
$CL/F_{,ss}$ [L/h]	NA	NA	1.06	(61.1)	1.08	(48.1)	0.997	(98.5)

* Median (min-max); NA = not applicable
* gMean: geometric mean, gCV: geometric CV

Dose Proportionality

Dose proportionality was observed over the entire weight-based dose range (0.001-0.008 mg/kg). The weight-based dosing scheme used in Studies 527.66 and 527.51 was instrumental in providing appropriate exposure to tamsulosin HCl in pediatric patients.

PK/PD Relationship Assessment

The relationship between PK parameters and PD parameters was explored graphically in the PK substudy of Study 527.66 for actual detrusor LPP and change from baseline in LPP at steady state for both $AUC_{\tau,ss}$ and $C_{max,ss}$. No clear relationship was observed between PK parameters and PD parameters after two weeks of treatment at the randomized dose level.

Population PK

Population PK (pop PK) analysis was conducted to describe the PK in pediatrics with neuropathic bladder (Studies 527.66 and 527.51) or without neuropathic bladder (Study 527.49: not reviewed since it was conducted in a different target population) and to identify clinical relevant covariates for the target patient population. This pop PK analysis was conducted to support dosing recommendation for pediatric patients with neuropathic bladder. However, (b) (4)

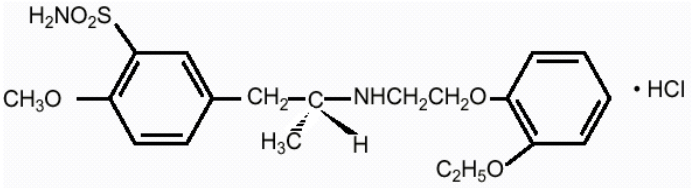
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is tamsulosin?

Tamsulosin is an α_1 adrenoceptor blocker that exhibits selectivity for α_{1A} receptors in the human prostate. Tamsulosin is indicated for the treatment of the signs and symptoms of BPH.

Tamsulosin HCl is (-)-(*R*)-5-[2-[[2-(*o*-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin HCl is a white crystalline powder that melts with decomposition at approximately 230°C. It is sparingly soluble in water and methanol, slightly soluble in glacial acetic acid and ethanol, and practically insoluble in ether. The empirical formula of tamsulosin HCl is $C_{20}H_{28}N_2O_5S{\cdot}HCl$. The molecular weight of tamsulosin HCl is 444.98 g/mol. Its structural formula is:



2.1.2 What is the regulatory history leading to this supplement?

Following the Sponsor's communicated intention to conduct a clinical development program to evaluate the efficacy and safety of tamsulosin in children and adolescents, discussions with the Agency were initiated on the precise population and indication.

A formal WR was sent to Boehringer Ingelheim Pharmaceuticals, Inc. on January 10, 2006. The WR was regarding the assessment of pediatric indication for treatment of pediatric patients (2-16 years of age) with elevated detrusor leak point pressure (LPP) associated with a known neurological disorder (e.g., spina bifida) and the development of an age-appropriate formulation for the proposed pediatric indication.

The tamsulosin HCl WR was formally amended on three separate occasions. The three formal amendments to the original WR were made dated March 20, 2006, October 18, 2006, and May 3, 2007, respectively. The first amendment was on March 20, 2006. This amendment served to clarify the distribution of patients within each of the two studies by weight and age. The second amendment was on October 18, 2006 and specified that Day 1 pharmacokinetics (PK) could be characterized in at least 9 patients (rather than all patients) who were reasonably distributed across three body weight ranges of Study 1 (Study 527.66). The third and final amendment to the WR was on May 3, 2007 and included the important agreement that the WR Study 1 could continue and Study 2 (Study 527.51) could be initiated in advance of the Division completing their review of the initial PK/Pharmacodynamics (PD) portion of Study 1. The agreed upon timeframe for submitting reports from these studies to the Agency was on or before July 1, 2009. The Sponsor met the agreed timeline for submission and the studies were conducted according to the written agreement. As a result, the pediatric exclusivity board has granted pediatric exclusivity to the Sponsor on September 17, 2009.

2.1.3 What is included in this supplement?

The Sponsor's response to the tamsulosin HCI WR is submitted as a supplemental new drug application (sNDA) with clinical data (SE-8) to the Flomax® NDA 20-579 including labeling. This labeling sNDA is intended to support two objectives. The first is to provide complete information and appropriate proposed pediatric labeling in response to the WR. As a result, this submission includes clinical study reports of Studies 527.55 and 527.61 which were the components of the WR. The second objective is to take the opportunity and reformat the Flomax® package insert in order to establish compliance with the Physician's Label Rule (PLR) (21 CFR 201.57).

2.2 General Clinical Pharmacology and Biopharmaceutics

2.2.1 What Clinical Pharmacology and Biopharmaceutics related information have been submitted to support this NDA supplement?

The original submission contained the following:

- Draft labeling in PLR format
- Information on the composition of drug products used in the pediatric clinical studies
- Full clinical study report of Studies 527.66 and 527.51 (Please note that there was no separate PK study report for Study 527.51)
- Population PK (pop PK) report for Studies 527.66 and 527.51

In addition, the Sponsor has submitted the following additional information:

- September 30, 2009: Clinical PK study report for Study 527.66.
- October 1, 2009:
  - Information on the components of the Flomax® and Omnic® products, and the placebo used in Studies 527.66 and 527.51.
  - Pop PK files (data sets, code files, and output files).
- October 2, 2009: Validation reports for the bioanalytical methods used in Studies 527.66 and 527.51.
- October 15, 2009: Bioanalytical study report of Study 527.66 (Section 16.1.9.2 of the clinical study report).

2.2.2 What is the dosing regimen and instructions of the pediatric formulation?

(b) (4)

2.2.3 What is the quantitative composition of the drug products used in the clinical trials of this supplement? Is the pediatric formulation adequately bridged with the Flomax® intact capsules?

Tamsulosin HCl Capsules, 0.025 mg, 0.1 mg, and 0.2 mg were developed to provide an age-appropriate formulation for the pediatric population. The development of the pediatric formulation included multi-national studies; therefore, it was necessary to use an alternate formulation of tamsulosin capsules in some participating countries. The alternate formulation is approved under the trademark of Omnic® in Europe and is identical to Flomax® with the exception of a small amount of the excipient, calcium stearate, which is used as (b) (4)

The comparison of Flomax® and Omnic® formulations had been previously discussed with the Division during a January 12, 2005 Guidance meeting. The issue was noted in the final meeting minutes issued on February 9, 2005. The Division had accepted the Sponsor's strategy for establishment of equivalence between Flomax® and Omnic® on the basis of comparative dissolution data supported by high solubility and permeability data. Discussion on this topic is captured in the Type C Guidance held on November 24, 2008 (meeting minutes dated December 22, 2008 in DARRTS under IND 30,365). To confirm the equivalency of the dissolution profiles for Flomax® and Omnic®, the dissolution profiles were generated using the regulatory specification for the dissolution test, 2 hrs in Stage I acidic buffer followed by dissolution on phosphate buffer pH 7.2. Dissolution profiles were also generated in three buffers, i.e., pH 1.2, 4.5, and 6.8 medium according to the SUPAC-MR Guidance requirements (Information submitted by the Sponsor on November 21, 2008 as IND 30,365 / SDN 430). Equivalency was established by achieving multi-point dissolution similarity scores (f_2) of > 50 with results obtained for both products using three different dissolution media (per Dr. David Lewis' CMC review for NDA 20-579 / S-025 dated June 4, 2009 available in DARRTS).

In addition, a BE study (Study ARI10021, submitted under NDA 21-319/S-014, approved on June 19, 2008) comparing Omnic® 0.4 mg and Flomax® 0.4 mg under fasting condition showed that they are bioequivalent (information on this can be found in Dr. George Benson's Division Director/Cross Discipline Team Leader Review dated June 18, 2008 under NDA 21-319/S-014 available to public at: http://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2008/021319se1-014_SUMR.pdf).

The quantitative composition of each component of the drug product is shown in Tables 2, 3, and 4 below:

Table 2: Comparative Quantitative Composition of Omnic® and Flomax®, 0.4 mg Capsules

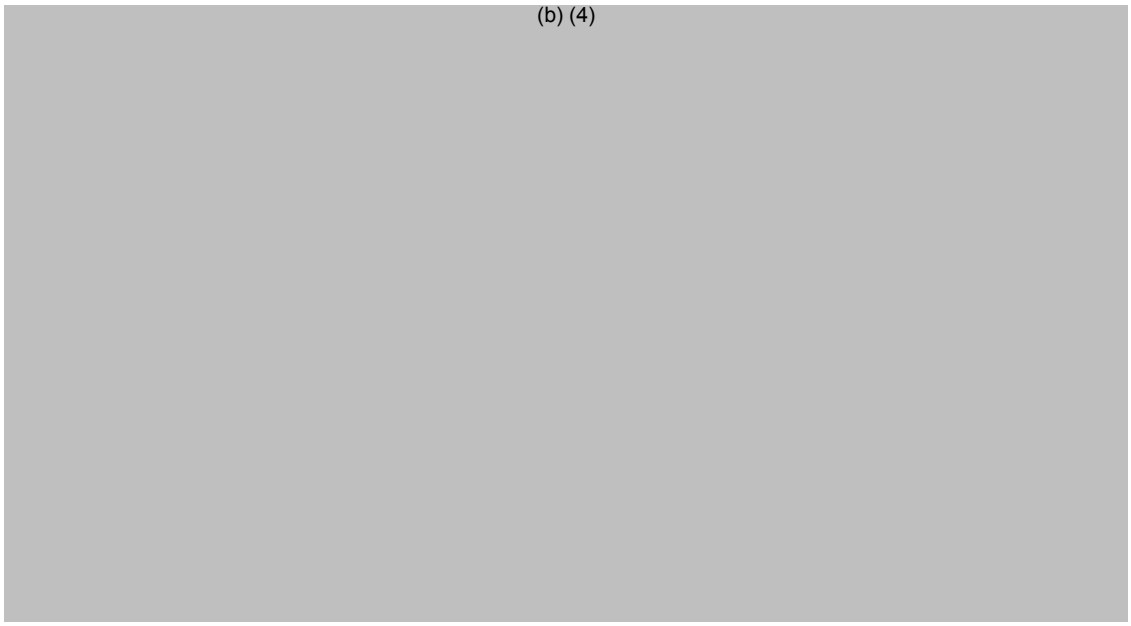


Table 3: Qualitative and quantitative composition of Tamsulosin HCl capsules (0.025 mg, 0.1 mg and 0.2 mg) used in the US

Table 4: Qualitative and quantitative composition of Placebo capsules used

Information regarding the effect of mixing the granules with applesauce or other fruit sauces or yogurt on drug release was submitted on April 4, 2006 (IND 30,356, SN 262) and September 25, 2006 (IND 30,365, SN 265). In the April 4, 2006 submission, the Sponsor submitted detail information on formulation development of active and placebo clinical capsules and information regarding the effect of mixing the granules with applesauce on drug release. Also, the Sponsor provided the in-use stability results for granules removed from tamsulosin capsules (with and without mixing) with applesauce over a 1 hr period. In the subsequent submission on September 25, 2006, the Sponsor submitted information pertaining to the appropriateness of mixing tamsulosin HCl granules with acidic soft foods such as applesauce, other fruit sauces, or yogurt. These were assessed by comparing the dissolution profile of the tamsulosin HCl intact capsules, granules alone and granules in applesauce or other fruit sauces or yogurt. Granules were determined to be incompatible with liquids or foods above pH 5 (e.g., water or foods such as pudding, rice pudding, milk, or Jello).

The Division concurred that the proposed all applesauce/tamsulosin pellets approach eliminates the need of BE demonstration between Flomax® intact capsules and the applesauce formulation as long as the PK associated with the applesauce/tamsulosin pellets formulation is adequately characterized (per Dr. Sandhya Apparaju's review, February 8, 2006).

2.2.4 What labeling changes are proposed in this supplement?

Upon completion and analysis of the results from the safety and efficacy trial, Study 527.51 (WR study 2), it was determined by the Sponsor that efficacy in the targeted pediatric population could not be supported. While the efficacy results from Study 527.51 do not support the pursuit of a formal indication, the Sponsor is proposing to include additional text within the package insert Section 8.4 entitled, "*Specific Population: Pediatric Use.*" The text briefly outlines the two clinical studies that were conducted in the targeted pediatric population and present both the conclusion that efficacy had not been established as well as the most frequent adverse events observed in the studies. No PK data were proposed to be added. The Sponsor is also proposing to reformat the Flomax® package insert to establish compliance with the PLR (21 CFR 201.57).

2.2.4 What are the PK parameters of Flomax® in pediatric population following single dose and multiple dose administration?

Study 527.66 (WR Study 1), an uncontrolled, open-label, titration study of tamsulosin HCl in children of either gender (ages 2-16 years) with neuropathic bladder, with a randomized PK sub-study investigating low, medium, and high weight-based (mg/kg) dose ranges, was conducted to characterize the PK/PD profile and evaluate the long term safety (up to 12 months) and efficacy of tamsulosin HCl in children with an elevated detrusor LPP associated with a known neurological disorder (e.g., spina bifida). Tamsulosin HCl was given once daily 30 min after breakfast up to 12 months. Upon completion of the PK section (i.e., Dose 14), these patients were allowed to continue in the open label portion of the trial for a full year. Subjects in this study were randomized to one of the three weight groups (i.e., 12.1-25 kg, 25.1-50 kg, or 50.1-100 kg) and was given tamsulosin HCl at one of the five dose levels (i.e., 0.025, 0.05, 0.1, 0.2, or 0.4 mg) that is appropriate for each weight-based (mg/kg) dose range (low, medium, or high) based upon their weight. A total of 31 patients were randomized into this PK substudy. Only 30 patients actually received study drug and were stratified by stratified by weight (12.1-25 kg, 25.1-50 kg, and 50.1-100 kg) and randomized into one of three weight-based dose levels of tamsulosin HCl; Low Dose level (Group L), Medium Dose level (Group M), and High Dose level (Group H). One patient discontinued from the study due to an adverse event (orthostatic

hypotension). There were, therefore, 29 patients in the steady state PK and PK/PD analyses. A summary of the PK results from Study 527.66 is shown in Table 5.

Table 5: Summary of PK Parameters of Tamsulosin after Single and Multiple Oral Administrations (Study 527.66)

	Single dose		Steady state					
	Low dose (0.001-0.002 mg/kg) (N=11)		Low dose (0.001-0.002 mg/kg) (N=10)		Medium dose (0.002-0.004 mg/kg) (N=9)		High dose (0.004-0.008 mg/kg) (N=10)	
	gMean	(gCV(%))	gMean	(gCV(%))	gMean	(gCV(%))	gMean	(gCV(%))
$C_{max,1}$ [ng/mL]	1.67	(68.8)	NA	NA	NA	NA	NA	NA
$C_{max,ss}$ [ng/mL]	NA	NA	2.79	(59.5)	5.02	(94.8)	14.1	(50.3)
$AUC_{\tau,ss}$ [ng·h/mL]	NA	NA	35.8	(75.6)	68.2	(94.7)	175	(61.0)
$t_{max,1}$* [h]	6.00	(2.00-8.00)	NA	NA	NA	NA	NA	NA
$t_{max,ss}$* [h]	NA	NA	5.00	(2.33-8.00)	5.92	(2.00-8.00)	5.01	(2.23-8.00)
$t_{1/2,ss}$ [h]	NA	NA	11.8	(48.1)	10.3	(40.8)	14.0	(31.9)
CL/F_{ss} [L/h]	NA	NA	1.06	(61.1)	1.08	(48.1)	0.997	(98.5)

* Median (min-max); NA = not applicable
* gMean: geometric mean

In addition, the Sponsor conducted Study 527.51 entitled, "A Phase 2b/3, multi-centre, double blind, randomized, placebo controlled, dose ranging study of tamsulosin HCl (low, medium, and high dose) as treatment in children with neuropathic bladder for three months" for the following objectives:

- To evaluate the efficacy of tamsulosin HCl over a range of doses, for the primary endpoint, percentage of patients who achieve reduction of LPP below 40 cm H_2O, in pediatric patients (2-16 years of age) with elevated detrusor LPP associated with a known neurological disorder (e.g. spina bifida).
- To determine the safety and tolerability of a range of dose levels of tamsulosin HCl as treatment in pediatric patients (2-16 years of age) with elevated detrusor LPP associated with a known neurological disorder (e.g., spina bifida).
- To characterize the pop PK of tamsulosin in the target population using a sparse sampling strategy: Characterize the systemic tamsulosin exposures and explore the effects of covariates including age, gender, race, body weight, AAG on the resultant PK.

Sparse PK sampling occurred at the following visits:

- Visit 5 (Day 42): pre-dosing and 2 hrs after taking the first sample
- Visit 6 (Day 70): more than 6 hrs after dosing and 2 hrs after taking the first sample

The protocol for Study 527.51 (WR Study 2) was determined to be consistent with the description provided within the WR. The Sponsor completed Study 527.51 with more than the requested number of patients (required: 120, actual: 161 total) within each subgroup (required: approximately 30 in each dose group, actual: > 38 in each dose group) defined within the WR.

There was no stand alone PK report submitted for Study 527.51.

2.2.5 What information was obtained from the population PK analysis?

Pop PK analysis was conducted to describe the PK in pediatrics with neuropathic bladder (Studies 527.66 and 527.51) or without neuropathic bladder (Study 527.49: not reviewed since it was conducted in a different target population) and to identify clinical relevant covariates for the target patient

population. This pop PK analysis was conducted to support dosing recommendation for pediatric patients with neuropathic bladder. However, this indication is not being pursued anymore due to the failure of supporting efficacy

Covariate analysis revealed that body weight and alpha-1 acid glycoprotein (AAG) had effects on both clearance and volume of distribution. No other intrinsic factors including gender, race (White vs. Asian), population (healthy subjects vs. patients) or extrinsic factors (co-medication of anti-cholinergic) showed significant effect on PK. Dose-normalized observed concentration vs. body weight profile showed that the pediatric PK is significantly affected by body weight especially for the younger population (outliers with higher dose normalized concentrations < 40 kg) even with weight-based dose adjustment in these populations.

2.2.6 Did the Sponsor use validated bioanalytical assays to generate the study data?

Yes. The bioanalytical method involved reverse phase liquid chromatography with tandem mass spectrometric detection. The analytical procedure in human plasma was shown to be linear in the dynamic range of 0.1 to 50.0 ng/ml (weighting factor $1/x^2$). This bioanalytical method was validated at (b) (4) and described in the (b) (4) Standard Operating Procedure no. 1237, version h.

In Study 527.66, a total of 465 study samples (282 samples corresponding to aliquot 1 and 183 samples corresponding to aliquot 2) were received from (b) (4) (b) (4) and (b) (4) (b) (4) between December 7, 2006 and June 10, 2007 (11 deliveries). The study samples were stored in a freezer at -75±10°C. Stability for tamsulosin in human plasma at approximately -70ºC for 108 days has been established in the process of method validation. The bioanalytical assay had the following preset acceptance criteria. All acceptance criteria were in compliance with the *Bioanalytical Method Validation Guidance* and were met.

Appendix

A.1. Individual Study Review

A.1.1. Study 527.66

An Uncontrolled, Open-label, Titration, Long-term Safety (up to 12 months) and Efficacy Study of Tamsulosin Hydrochloride in Children with Neuropathic Bladder, with a Randomized Pharmacokinetic Sub-study Investigating Low, Medium and High Dose Ranges

Protocol No:	527.66
Phase: 2	
Principal Investigator:	Jeffrey B. Campbell, M.D.
Clinical Study Center:	Department of Urology, University of Oklahoma Health Sciences Center, Oklahoma City, OK
Clinical Study Dates:	May 9, 2006 - June 6, 2007
Analytical Study Facility:	(b) (4)
Analytical Study Dates:	December 15, 2006 - June 18, 2007

OBJECTIVE

The objective of the study was to characterize the PK/PD profile and evaluate the safety and efficacy of tamsulosin HCl in children with an elevated detrusor LPP associated with a known neurological disorder (e.g., spina bifida). Upon completion of the PK section (i.e., Dose 14), these patients were allowe to continue in the open label portion of the trial for a full year.

STUDY DESIGN, TREATMENT, AND SUBJECTS

This was an open-label, multi-center, randomized (in a subset of patients), dose-titration trial without a control group, in which children with neuropathic bladders were entered. There are two different groups of patients described in the study protocol; those who participated in the PK section and those who did not. This review covers only those patients who participated in the PK section of the trial.

The patient inclusion criteria included the following:

- Children of either gender; ages (2-16 years) inclusive. Only patients with a body weight of between 12.1 and 100 kg were allowed to participate in the PK section.
- Neuropathic bladder secondary to myelodysplasia (including transverse myelopathy, myelomeningocele, sacral agenesis, tethered cord syndrome, etc.), spinal cord tumor or spinal cord trauma. This included patients who are performing clean intermittent catheterization (CIC).
- Elevated detrusor LPP $\geq$ 40 cm H_2O confirmed by two measurements at baseline. An LPP recorded while on stable medication and within 3 months prior to starting this study could be allowed as the baseline measurement if this recording was confirmed by two measurements.

A total of 31 patients were randomized into this PK substudy. Only 30 patients actually received study drug and were stratified by stratified by weight (12.1-25 kg, 25.1-50 kg, and 50.1-100 kg) and randomized into one of three weight-based dose levels of tamsulosin HCl; Low Dose level (Group L), Medium Dose level (Group M), and High Dose level (Group H). Upon completion of the PK section, these patients were allowed to continue in the open label portion of the trial for a full year. Patients

with a body weight between 9 kg and 12 kg were not to be entered into the PK section of this study as it was not possible to randomize them into the three predetermined dose levels. For these patients the Low Dose level was not available, as the smallest available capsule strength for tamsulosin HCl was 0.025 mg. Therefore, these low weight patients were enrolled into the open label efficacy and safety section of the trial and started at the Medium Dose level and titrated to High Dose level if needed. Patient 1194 was randomized, treated, and prematurely discontinued from the study due to an adverse event (orthostatic hypotension). There were, therefore, 29 patients in the steady state PK and PK/PD analyses.

The mean age among all patients in the Treated set was 8.0 years and was comparable among all three treatment groups (low-dose, 8.7 years; medium-dose, 6.5 years; high-dose, 8.8 years). Only five patients (16.7%) entered into the study with ages between 2-5 years. Most of the patients that were entered into the study had ages between 5-10 years (14 patients [46.7%]) and 10–16 years (11 patients [36.7%]). All patients within the Treated set were between the ages of 2 and 15 years. Most of the patients were classified as being either White (56.7%) or Asian (43.3%). Although the two races were represented in each of the dose groups, the medium dose group had substantially more Whites (8 patients [80%]) represented in the group as compared to the Asian patients (2 patients [20%]). The mean weight of patients that entered into the study was 31.6 kg. Mean weights for each of the randomized dose groups were comparable. Only four patients (13.3%) entered into the study with weights between 50.1-100 kg. Most of the patients that were entered into the study had body weights between 12.1-25 kg (14 patients [46.7%]) and 25.1-50 kg (12 patients [40%]). There were a higher percentage of males than females represented in the total Treated set (56.7% and 43.3%, respectively). Of the three dose groups the medium dose group had more disproportion of males (7 patients [70%]) represented in the group as compared the females (3 patients [30%]).

Table A-1: Number of Patients Randomized by Weight into Each Dose Group – Treated set

Weight (kg)	Tams-low	Tams-medium	Tams-high	Total
12.1-25 kg (Low Weight)	5	5	4	14
25.1-50 kg(Medium Weight)	4	4*	4	12
50.1-100 kg (High Weight)	1	1	2	4
Total	10	10	10	30

* This includes one male patient (1194) who was randomized, treated and prematurely discontinued from the study due an AE before reaching his randomize dose.

Table A-2: Demographics and Baseline Characteristics – treated set

	Tams-low	Tams-medium	Tams-high	Total
Number of patients	10(100.0)	10(100.0)	10(100.0)	30(100.0)
Gender [N(%)]				
Male	5(50.0)	7(70.0)	5(50.0)	17(56.7)
Female	5(50.0)	3(30.0)	5(50.0)	13(43.3)
Age [years]				
N	10	10	10	30
Mean	8.7	6.5	8.8	8.0
SD	4.5	2.6	3.7	3.7
Min	2	3	4	2
Median	9.0	6.5	8.5	7.0
Max	15	12	15	15
Age group [N(%)]				
2-<5 years	2(20.0)	2(20.0)	1(10.0)	5(16.7)
5-<10 years	3(30.0)	7(70.0)	4(40.0)	14(46.7)
10-16 years	5(50.0)	1(10.0)	5(50.0)	11(36.7)
Race [N(%)]				
Amer.Ind./Alaska Nat	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Asian	5(50.0)	2(20.0)	6(60.0)	13(43.3)
Black/African Amer.	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Hawaiian/Pacif. Isle	0(0.0)	0(0.0)	0(0.0)	0(0.0)
White	5(50.0)	8(80.0)	4(40.0)	17(56.7)
Hispanic/ Latino [N(%)]				
No	9(90.0)	10(100.0)	10(100.0)	29(96.7)
Yes	1(10.0)	0(0.0)	0(0.0)	1(3.3)
Concomitant anti cholinergic use [N(%)]				
No	8(80.0)	7(70.0)	9(90.0)	24(80.0)
Yes	2(20.0)	3(30.0)	1(10.0)	6(20.0)
Weight [kg]				
N	10	10	10	30
Mean	32.76	31.38	30.56	31.57
SD	22.94	21.98	15.24	19.65
Min	12.1	15.4	15.0	12.1
Median	27.50	25.60	27.00	26.65
Max	91.0	92.2	57.0	92.2
Weight group [N(%)]				
9-<12.1 kg	0(0.0)	0(0.0)	0(0.0)	0(0.0)
12.1-<25.1 kg	5(50.0)	5(50.0)	4(40.0)	14(46.7)
25.1-<50.1 kg	4(40.0)	4(40.0)	4(40.0)	12(40.0)
50.1-100 kg	1(10.0)	1(10.0)	2(20.0)	4(13.3)

All laboratory evaluations, assignment of randomized treatment for the PK section and interpretation of ECGs were performed by centralized facilities. All bioanalytical assays for the PK section were performed by (b) (4) (b) (4).

DOSING RATIONALE

The data of the tamsulosin HCl from Study 527.2, an extended, long-term, open-label Phase 3b, multi-center clinical study of 0.4 mg QD and 0.8 mg QD of modified release tamsulosin HCl in patients with the signs and symptoms of BPH, conducted by the Sponsor shows that the body weight of the patients (n = 609) ranged from 52 kg to 156 kg. At the 0.4 mg tamsulosin HCl dose this would calculate to 0.0077 mg/kg to 0.0026 mg/kg, and at the 0.8 mg tamsulosin HCl dose the calculation ranges from 0.0154 mg/kg to 0.0051 mg/kg.

Based on this mg/kg exposure range in adults, a dosing scheme for children was developed. For additional safety, there are three active treatment groups (a Low, Medium, and a High Dose level). The actual dose to be received was based upon three weight groups: 12.1 to 25 kg, 25.1 kg to 50 kg, and 50.1 to 100 kg. Table A-3 reflects the calculated dose levels based on ranges of mg/kg tamsulosin HCl doses over the three proposed weight groups.

Table A-3: Calculated Tamsulosin HCl Dose Levels for Weight Groups

Weight (kg)	Low Dose level (0.001 – 0.002 mg/kg)	Medium Dose level (0.002 – 0.004 mg/kg)	High Dose level (0.004 – 0.008 mg/kg)
12.1 – 25.0	0.012 mg to 0.050 mg	0.024 mg to 0.100 mg	0.048 mg to 0.200 mg
25.1 – 50.0	0.025 mg to 0.100 mg	0.050 mg to 0.200 mg	0.100 mg to 0.400 mg
50.1 – 100.0	0.050 mg to 0.200 mg	0.100 mg to 0.400 mg	0.200 mg to 0.800 mg

In Study 527.66, tamsulosin HCl was administered once daily, in dosages of 0.025, 0.05, 0.1, 0.2, or 0.4 mg, 30 min after breakfast, with the contents of the capsules being sprinkled over a teaspoon of applesauce or yogurt, followed by a spoonful of water. A precise mg/kg-based scheme was not possible due to the MR formulation characteristics of tamsulosin HCl capsules. Based upon the available dosage strengths individual doses have been selected to meet these mg/kg dose levels based upon the weight of the child as listed in Table A-4 below.

Table A-4: Proposed Tamsulosin HCl Dosing Schema for Study 527.66

Weight (kg)	Low Dose level (0.001 – 0.002 mg/kg)	Medium Dose level (0.002 – 0.004 mg/kg)	High Dose level (0.004 – 0.008 mg/kg)
12.1 – 25.0	0.025 mg	0.05 mg	0.1 mg
25.1 – 50.0	0.05 mg	0.1 mg	0.2 mg
50.1 – 100.0	0.1 mg	0.2mg	0.4 mg

FORMULATION

Tamsulosin HCl 0.025, 0.1, and 0.2 mg. MR, non-branded capsules were supplied from (b) (4) Medication bottles containing the different dosages have color coded labels to assist with the administration and dispensing of the correct dose strength. All patients received their medication dose via opened capsules with the contents sprinkled over applesauce or yogurt. Tamsulosin HCl Capsules, 0.025 mg, 0.1 mg, and 0.2 mg were developed to provide an age-appropriate formulation for the pediatric population. The development of the pediatric formulation included multi-national studies; therefore, it was necessary to use an alternate formulation of tamsulosin capsules in some participating countries. The alternate formulation is approved under the trademark of Omnic® in Europe and is identical to Flomax® with the exception of a small amount of the excipient, calcium stearate, which is used as (b) (4) A BE study (Study ARI10021, submitted under NDA 21-319/S-014, approved on June 19, 2008) comparing Omnic® 0.4 mg and Flomax® 0.4 mg under fasting condition showed that they are bioequivalent (information on this can be found in Dr. George Benson's Division Director/Cross Discipline Team Leader Review dated June 18, 2008 under NDA 21-319/S-014 available to public at:
http://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2008/021319se1-014_SUMR.pdf).

- Substance (INN): Tamsulosin HCl
- Pharmaceutical form: Capsule
- Batch number: - U.S. Supplies: 617ET001N02;617FT001N02; 617GT001N02

- Source: (b) (4)
- Unit strength: 0.025 mg, 0.1 mg or 0.2 mg
- Daily dose: 0.025 mg, 0.05 mg, 0.1 mg, 0.2 mg, or 0.4 mg once daily dependent on a patient's body weight
- Duration of use: Up to 12 months
- Route of administration: Oral
- Regimen: Contents of opened capsules sprinkled over applesauce or yogurt, taken 30 minutes after breakfast.

The components of the different formulations are summarized in Tables A-5, A-6, and A-7 below:

Table A-5: Comparative Quantitative Composition of Omnic® and Flomax®, 0.4 mg Capsules

(b) (4)

Table A-6: Qualitative and Quantitative Composition of Tamsulosin HCl Capsules used in the US (Flomax®)

(b) (4)

Table A-7: Qualitative and quantitative composition of Placebo capsules used

(b) (4)

PHARMACOKINETIC EVALUATION

Blood sampling

A total of 13 (1 ml each) blood samples were drawn per subject contributing to the PK section. For quantitation of drug plasma concentrations, 1 ml of venous blood was taken into standard blood collection tubes (plastic, no gel allowed) containing lithium-heparin as anticoagulant and labeled appropriately at the following time points:

Table A-8: Blood Sampling Schedule for PK Analysis

Day	Time
Day 1	15 minutes prior to dose administration and then 2, 4, 6 and 8 hours after first drug administration
Day of dose 14 of randomized level	15 minutes prior to dose administration and then 2, 4, 6, 8 and 10 hours after drug administration
Day after dose 14 of the randomized level	24 and 33(±3) hours after the last drug administration

Concomitant Therapy

Concomitant therapy was not permitted during the conduct of this trial. If a patient was receiving medication(s) prior to the commencement of the trial for the treatment of a medical condition other than the study indication, such medication(s) may be continued for the duration of the trial at the discretion of the investigator. It was the responsibility of the investigator to ensure that all changes in medication for a patient were recorded in full on the electronic case report form. Drugs with systemic anticholinergic activity including antihistamines were allowed if the dose was stable for a minimum of 30 days prior to Visit 1.

Bioanalytical method

The bioanalytical method involved a liquid-liquid extraction with ethyl acetate/cyclohexane (75/25; v/v) followed by reverse phase liquid chromatography with tandem mass spectrometric detection. The analytical procedure in human plasma was shown to be linear from 0.100 to 50.0 ng/ml (weighting factor $1/x^2$) using 0.20 ml of sample. This bioanalytical method was previously validated at (b) (4) and described in the (b) (4) Standard Operating Procedure no. 1237, version h.

Tamsulosin HCl was obtained from (b) (4) (b) (4) (batch number ARS 05-03-SS-04, expiry date March 31, 2007 and batch number ARS 06-10-SS-04, expiry date October 1, 2008). The purity of the material was assumed to be 100 %. The molecular weight was 444.97 g/mol. The analytical reference standard was stored in a refrigerator at 5±5°C in a flask protected from light and humidity. The stability of tamsulosin HCl stock solutions was demonstrated over a 135 day period of storage in a freezer room at -24±6°C in a flask protected from light. (b) (4) the internal standard of tamsulosin hydrochloride, was obtained from (b) (4) (b) (4) (batch number T-4912, expiry date February 28, 2011). The purity of the material was assumed to be 100%. The molecular weight was 422.20 g/mol. The analytical reference standard was stored in a refrigerator at 5±5°C. The stability of (b) (4) stock solutions was demonstrated over a 15 day period of storage in a freezer room at -24±6°C in a flask protected from light.

A total of 465 study samples (282 samples corresponding to aliquot 1 and 183 samples corresponding to aliquot 2) were received from (b) (4) (b) (4) and (b) (4) (b) (4) between December 7, 2006 and June 10, 2007 (11 deliveries). The number of samples agreed with the

documentation provided with the samples. The study samples were stored in a freezer at -75°C±10°C. Stability for tamsulosin HCl in human plasma at approximately -70ºC for 108 days has been established in the process of method validation.

The study samples were assayed by batch with 8 calibration standards including one level corresponding to the lower limit of quantitation (LLOQ: 0.100 ng/ml) and one level corresponding to the upper limit of quantitation (ULOQ: 50.0 ng/ml). Concentrations were determined using the slope and the intercept of the calibration line obtained by least square regression using the appropriate weighting factor ($1/x^2$). Each batch included six quality control (QC) samples (in duplicate) at three concentration levels: one near the lower limit of quantification (QC1: 0.300 ng/ml), one in the mid-range (QC2: 7.50 ng/ml) and one near the upper limit of quantification (QC3: 45.0 ng/ml).

The bioanalytical assay had the following preset acceptance criteria. Calibration standards were excluded from the final calibration line only if the back-calculated inaccuracy was greater than ±15% (±20% for the LLOQ), for reasons of instrument failure, unusual internal standard levels or documented problems during preparation or extraction. No more than 30% of the calibration standards may be excluded from each series of calibration standards and the final calibration line must contained at least 6 calibration concentration levels including the LLOQ and the ULOQ. The determination coefficient (r^2) must be greater than 0.98. The results of the QC samples provided the basis of accepting or rejecting the batch data. At least four QC samples out of six had to be within ±15% of their respective nominal values (two of the six, not both at the same concentration level, may be outside the ±15%). All acceptance criteria were in compliance with the *Bioanalytical Method Validation Guidance* and were met.

Table A-9: Performance of Calibration Standards for the Assay of Tamsulosin Hydrochloride (YM617) in Human Plasma, Obtained during the Analysis of the Study Samples

Run Date	Run Number	STD.1 [0.100 ng/mL]	STD.2 [0.200 ng/mL]	STD.3 [0.500 ng/mL]	STD.4 [1.00 ng/mL]	STD.5 [5.00 ng/mL]	STD.6 [10.0 ng/mL]	STD.7 [20.0 ng/mL]	STD.8 [50.0 ng/mL]
19-Dec-2006	2	0.106	0.176	0.463	1.00	4.92	10.2	21.3	50.5
19-Dec-2006	2	0.106	0.184	0.471	1.03	4.88	11.0	21.0	48.8
15-Jun-2007	4	0.100	0.183	0.493	0.934	5.17	10.4	21.4	55.0
15-Jun-2007	4	0.115	0.173	0.443	0.927	5.31	9.94	20.4	51.4
15-Jun-2007	5	0.0983	0.187	0.483	0.857	4.80	9.73	19.5	50.9
15-Jun-2007	5	0.107	*0.154	0.513	0.960	5.13	11.1	21.0	54.9
15-Jun-2007	6	0.106	0.198	0.454	0.934	5.07	10.3	21.1	51.9
15-Jun-2007	6	0.105	0.176	0.491	0.897	5.17	10.3	20.7	53.4
Mean		0.105	0.182	0.476	0.942	5.06	10.4	20.8	52.1
S.D.		0.00501	0.00854	0.0230	0.0548	0.174	0.473	0.614	2.18
Imprecision (%)		4.77	4.69	4.83	5.82	3.44	4.55	2.95	4.18
Inaccuracy (%)		5.00	-9.00	-4.80	-5.80	1.20	4.00	4.00	4.20
n		8	7	8	8	8	8	8	8

*Bias >15%, value not included in statistics

Blank matrix samples were injected after the first series of calibration standards and after each high quality control sample in order to verify the carryover of each batch. No peak at the retention time of the analytes or the internal standards and in the relevant mass channel interfered with the analytes and the internal standards by more than 20% of the mean of the LLOQ calibration standard peak signals and by more than 5% of the mean internal standard peak signal. Therefore, it was concluded that there were no carryover issues.

Within each batch of study samples, all QC samples were within ±15% of their respective nominal values. For calculation of inaccuracy and imprecision, the rounded values of means and standard deviations were used. Data for inaccuracy and imprecision in human plasma are shown in Table A-10.

Table A-10: In-study Inaccuracy and Imprecision Data of Tamsulosin Hydrochloride Measurements in Human Plasma

Tamsulosin hydrochloride (YM617)	Name	Concentration [ng/mL]	n	Inaccuracy (%)	Imprecision CV (%)
In-study	QC.1	0.300	8	-3.67	7.40
	QC.2	7.50	8	3.60	5.37
	QC.3	45.0	8	6.67	4.25

Levels of tamsulosin HCl were determined in the plasma study samples received at (b) (4) and for which the analysis requirement was confirmed by the Sponsor. Analyses of the study samples were performed from December 19, 2006 to June 15, 2007. In total, 4 batches were analyzed and accepted. The retention times of tamsulosin HCl and of their internal standard were approximately 1.04 and 1.07 min, respectively.

DATA ANALYSIS

Pharmacokinetic Analysis

PK endpoints of the study include the following:

- $C_{max,1}$ (maximum measured concentration of the analyte in plasma following the first dose)
- $t_{max,1}$ (time from dosing to maximum measured concentration of the analyte in plasma after administration of the first dose)
- Dose- and weight-normalized $C_{max,1}$
- $C_{pre,ss}$ (pre-dose concentration of the analyte in plasma at steady state immediately before administration of the next dose)

The following PK parameters were determined after the last dose in the PK section of the study::

- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
- $t_{max,ss}$ (time from last dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
- $C_{min,ss}$ (minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)
- $\lambda_{z,ss}$ (terminal rate constant of the analyte in plasma at steady state)
- $t_{1/2,ss}$ (terminal half-life of the analyte in plasma at steady state)
- $MRT_{po,ss}$ (mean residence time of the analyte in the body at steady state after p.o. administration)
- Weight-normalized $CL/F_{,ss}$ (apparent clearance of the analyte in the plasma at steady state after extravascular multiple dose administration)
- Weight-normalized $V_z/F_{,ss}$ (apparent volume of distribution during the terminal phase λ_z at steady state following extravascular administration)
- Dose- and weight-normalized $C_{max,ss}$ and $AUC_{\tau,ss}$
- Accumulation ratios of the analyte in plasma following 14 doses over a uniform dosing interval τ were calculated for the Low Dose group: $R_{A,Cmax}$
- Assessment of dose proportionality: $C_{max,ss}$, $AUC_{\tau,ss}$

Weight normalization of $C_{max,1}$, $C_{max,ss}$, and $AUC_{\tau,ss}$ were performed by dividing the respective quantities by the reciprocal of body weight in kg. Weight-normalized $CL/F_{,ss}$ and $VzF_{,ss}$ were calculated by dividing the respective quantities by body weight in kg.

Statistical Analysis

Concentrations were used for calculations in the format that was reported in the bioanalytical study report. The data format for descriptive statistics of concentrations was identical with the data format of the respective concentrations. For the calculation of PK parameters, only concentrations within the validated concentration range were used. The descriptive statistics of PK parameters were calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics were reported with three significant digits in the clinical trial report. The actual sampling times were used. For pre-dose samples, the actual sampling time was set to zero. Noncompartmental PK parameters were determined using WinNonlin.

Safety Evaluations and Adverse Events

Safety evaluation included vital signs, physical exam, ECG, laboratory tests, and adverse events (AE) monitoring. No serious AE were reported during the study and no subjects were withdrawn from the therapy due to an adverse event. In this trial, the most common AEs (≥ 5% of subjects) were headache, nausea, nasopharyngitis, vaginal discharge, diarrhea, peripheral edema, weight increased, pharyngolaryngeal pain, back pain, metrorrhagia, vomiting, pain in extremity, haematoma, hot flash, phlebitis, flatulence, cough, fall, bronchitis, dizziness, and malaise. Two subjects were withdrawn from the study (both from Group CD), due to an increased Gamma-GT (GGT) before first dosing or non-compliance during early treatment period.

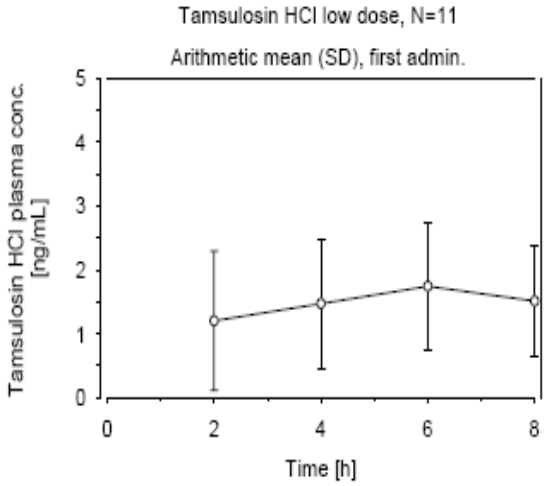
PHARMACOKINETIC RESULTS

PK profile after single dose

There were 11 evaluable patients who provided blood samples for the evaluation of plasma concentration profiles after the first dose. First dose PK sampling was made optional in Amendment No. 2 (October 18, 2006) and therefore no additional patients provided samples after these first 11 patients. All the patients received the low dose of tamsulosin HCl as the first dose since dose was uptitrated in this trial.

The arithmetic mean plasma concentration-time profile of tamsulosin HCl after first oral administration of low dose of tamsulosin HCl is shown in Figure A-1. The plasma concentration of tamsulosin HCl increased gradually after the administration and reached the peak at around 6 hrs.

Figure A-1: Arithmetic Mean Plasma Concentration-Time Profile of Tamsulosin HCl after First Oral Administration of Low Dose of Tamsulosin HCl



The median value of $t_{max,1}$ and the geometric mean value of $C_{max,1}$ after first oral administration of low dose of tamsulosin HCl were 6.00 hrs and 1.67 ng/ml, respectively.

PK profile after multiple doses

In the PK substudy there were 29 evaluable patients who provided blood samples for the analysis of plasma concentration profiles at steady state after multiple oral doses of tamsulosin HCl.

The plasma concentrations of tamsulosin HCl after multiple oral administrations of low, medium, and high dose (weight-based dose) of tamsulosin HCl increased gradually to the peak (median $t_{max,ss}$ of 5-6 hrs) and then declined with the half life of 10.3-14.0 hrs (Figure A-2).

Figure A-2: Arithmetic Mean Plasma Concentration-Time Profiles of Tamsulosin HCl after Multiple Oral Administrations of Tamsulosin HCl (all dose and weight groups)

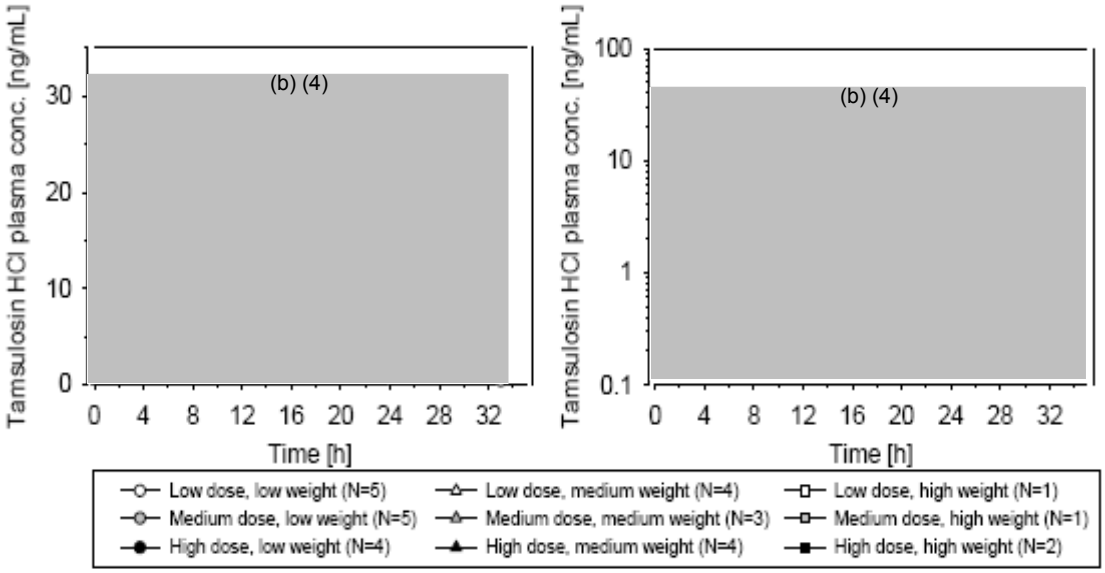
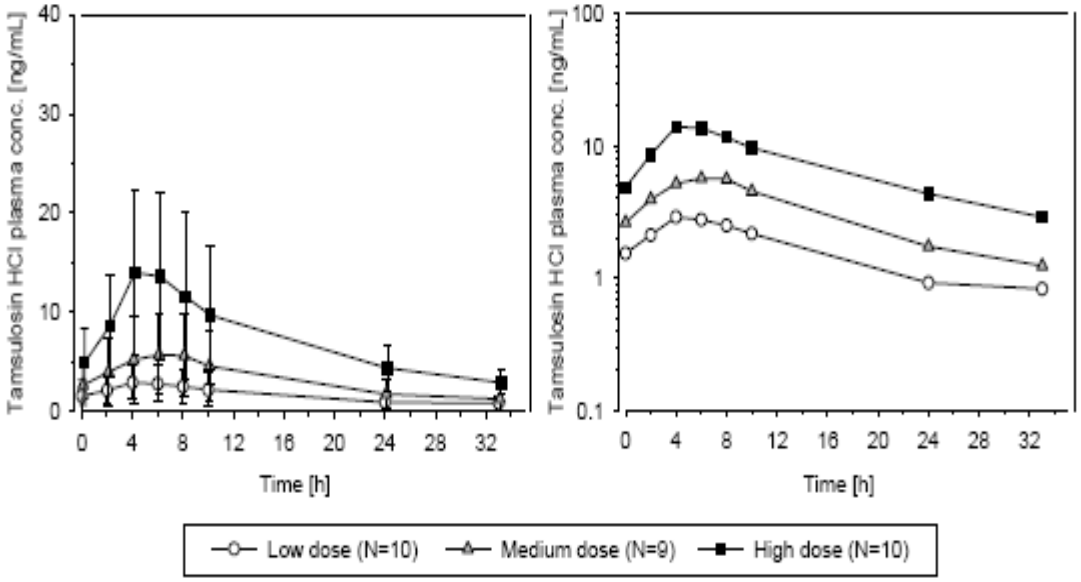


Figure A-3: Arithmetic Mean Plasma Concentration-Time Profiles of Tamsulosin HCl after Multiple Oral Administrations of Tamsulosin HCl



There were no apparent differences in PK parameters (i.e., median values of $t_{max,ss}$ and geometric mean values for all other parameters) such as $t_{max,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, and $Vz/F_{,ss}$ among weight-based dose groups (Table A-10). This result indicates that the basic PK profile of tamsulosin HCl in pediatric patients was consistent from low dose to high dose. The values of $C_{max,ss}$ and $AUC_{\tau,ss}$ increased with increasing dose (weight-based dose). In addition, both dose-normalized and dose- and weight-normalized $C_{max,ss}$ and $AUC_{\tau,ss}$ were comparable among dose groups.

Dose proportionality was investigated using a power model which describes the functional relationship between the dose per kg body weight and PK endpoints AUC and C_{max} at steady-state. Based on this analysis, the slope for the evaluation of $AUC_{\tau.ss}$ was 0.9800 with a 95% confidence interval (CI) of 0.59-1.37 and the slope for $C_{max.ss}$ was 1.0039 with a 95% CI of 0.65-1.36. Thus, this indicates dose proportionality of both of these parameters across the entire weight-based does range (0.001-0.008 mg/kg). These results indicate that the weight-based dosing scheme in this trial was appropriate to control the exposure to tamsulosin HCl in pediatric patients.

The values of $C_{max,ss}$ and AUCτ,ss increased with increasing dose (weight-based dose). Values of dose-normalized $C_{max,ss}$ ($C_{max,ss,norm}$) and $AUC_{\tau,ss}$ ($AUC_{\tau,ss,norm}$) were comparable among the dose groups (Table A-11). After further weight normalization, $C_{max,ss,norm.dw}$ and $AUC_{\tau,ss,norm.dw}$ were also comparable among the dose groups (Table A-11). The accumulation ratio was calculated from the patients who were randomized to the low dose group and for whom both parameters at first dose and steady state dose (n=4) were available. Individual accumulation ratios were variable and were (b) (4) for those four individuals. The geometric mean value of $R_{A,Cmax}$ was 1.58.

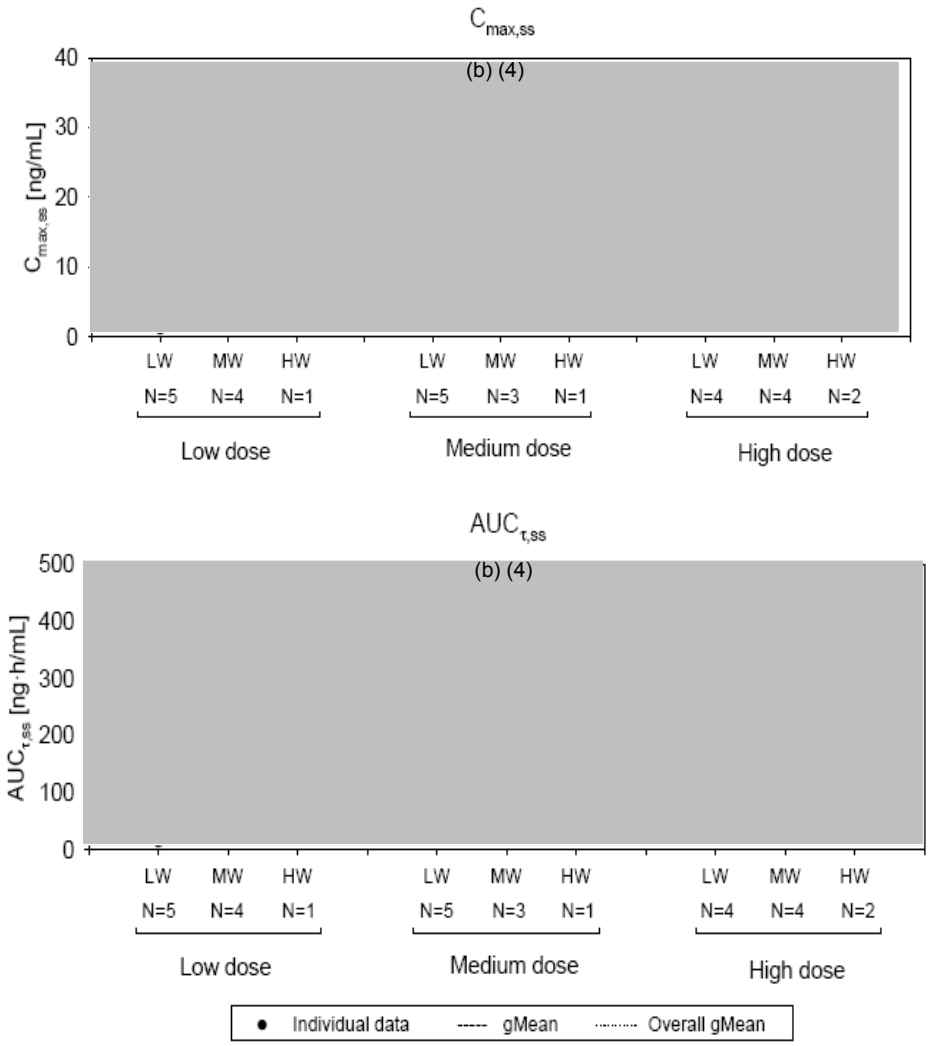
Table A-11: Summary of PK Parameters of Tamsulosin HCl after Multiple Oral Administrations of Tamsulosin HCl (each dose group)

	Summary pharmacokinetic parameters of tamsulosin HCl							
	Single		Steady state					
	Low dose (N=11)		Low dose (N=10)		Medium dose (N=9)		High dose (N=10)	
	gMean	(gCV(%))	gMean	(gCV(%))	gMean	(gCV(%))	gMean	(gCV(%))
$C_{max,1}$ [ng/mL]	1.67	(68.8)	NC	NC	NC	NC	NC	NC
$t_{max,1}$ [a)] [h]	6.00	(2.00-8.00)	NC	NC	NC	NC	NC	NC
$C_{max,ss}$ [ng/mL]	NC	NC	2.79	(59.5)	5.02	(94.8)	14.1	(50.3)
$AUC_{\tau,ss}$ [ng·h/mL]	NC	NC	35.8	(75.6)	68.2	(94.7)	175	(61.0)
$t_{max,ss}$ [a)] [h]	NC	NC	5.00	(2.33-8.00)	5.92	(2.00-8.00)	5.01	(2.23-8.00)
$C_{min,ss}$ [ng/mL]	NC	NC	0.747	(99.7)	1.52	(130)	4.01	(68.5)
$t_{1/2,ss}$ [h]	NC	NC	11.8	(48.1)	10.3	(40.8)	14.0	(31.9)
$MRT_{po,ss}$ [h]	NC	NC	18.7	(50.5)	17.6	(35.0)	20.9	(23.6)
$CL/F_{,ss}$ [L/h]	NC	NC	1.06	(61.1)	1.08	(48.1)	0.997	(98.5)
$V_z/F_{,ss}$ [L]	NC	NC	18.0	(51.6)	16.1	(76.2)	20.1	(143)
$C_{max,ss,norm,d}$ [ng/mL/mg]	NC	NC	73.7	(50.4)	68.3	(56.0)	81.2	(83.2)
$AUC_{\tau,ss,norm,d}$ [ng·h/mL/mg]	NC	NC	944	(61.1)	928	(48.1)	1000	(98.5)
$C_{max,ss,norm,d,w}$ [ng/mL/mg·kg]	NC	NC	2040	(74.3)	1850	(85.7)	2240	(47.6)
$AUC_{\tau,ss,norm,d,w}$ [ng·h/mL/mg·kg]	NC	NC	26100	(91.1)	25200	(82.9)	27700	(59.1)

a) Median (min-max); NC: Not calculated

The PK parameters among dose and weight groups after multiple oral doses of tamsulosin HCl are compared in Figure A-4. The exposure to tamsulosin HCl increased with increasing dose (weight-based dose).

Figure A-4: Comparison of pharmacokinetic parameters among dose and weight groups after multiple oral administrations of tamsulosin HCl



When the difference in actual dose per body weight is taken into consideration, there are no apparent differences in exposure to tamsulosin HCl between pediatric patients and adults. The relationships between PK parameters and PD parameters were explored graphically for actual detrusor LPP and change from baseline in LPP at steady state for both $AUC_{\tau,ss}$ and $C_{max,ss}$ (Figures A-5 through A-8). No clear relationship was observed either in LPP or in change from baseline in LPP after 2 weeks of treatment at the randomized dose level.

Figure A-5: PK/PD: Relationship between $AUC_{\tau ss}$ and Detrusor LPP

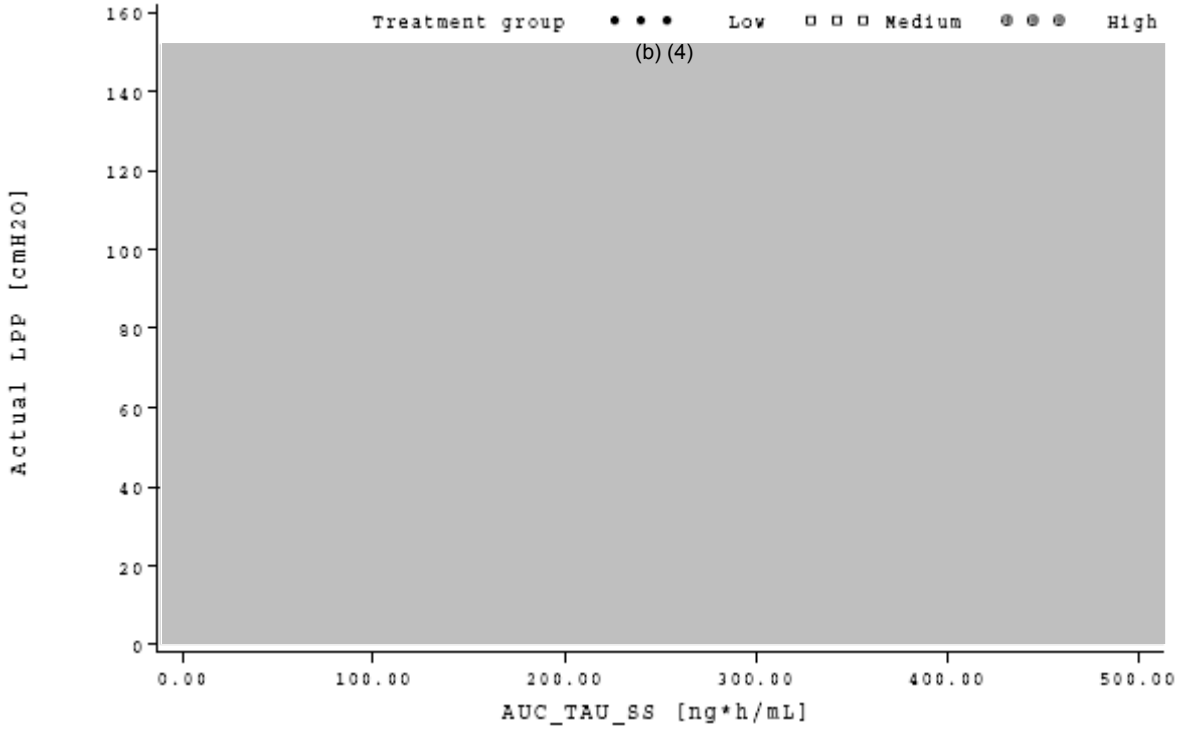


Figure A-6: PK/PD: Relationship between $C_{max\ ss}$ and Detrusor LPP

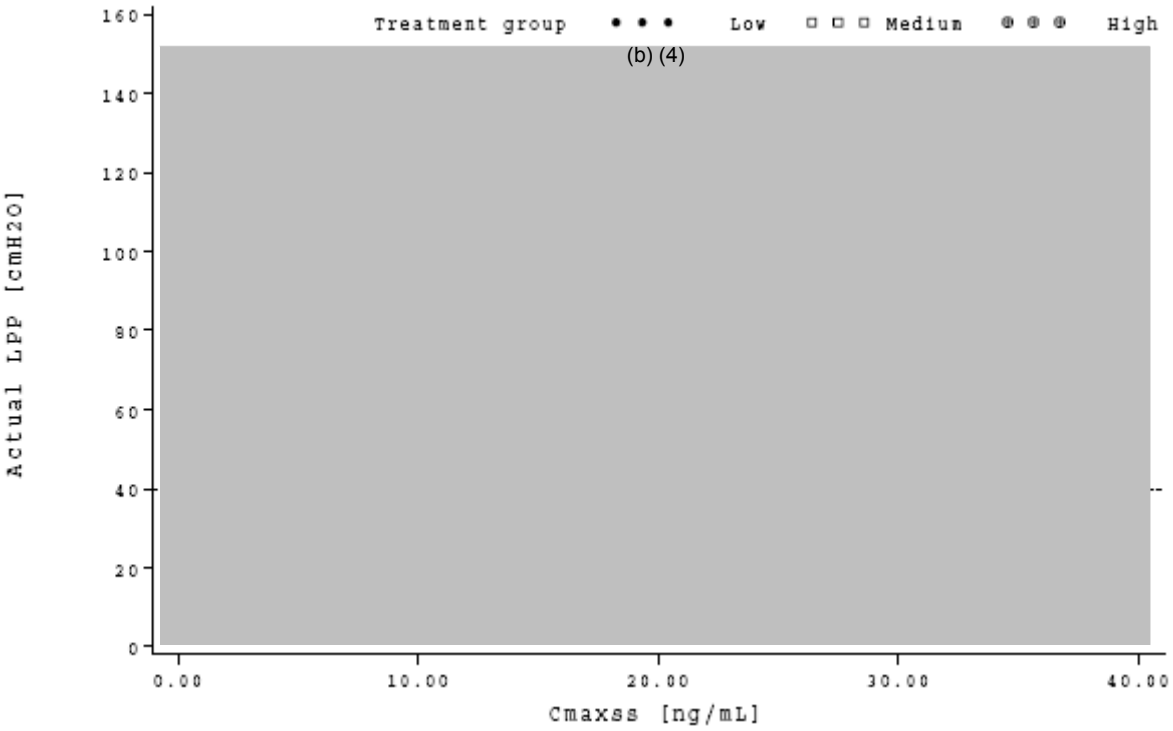


Figure A-7: PK/PD: Relationship between $AUC_{\tau ss}$ and Detrusor LPP

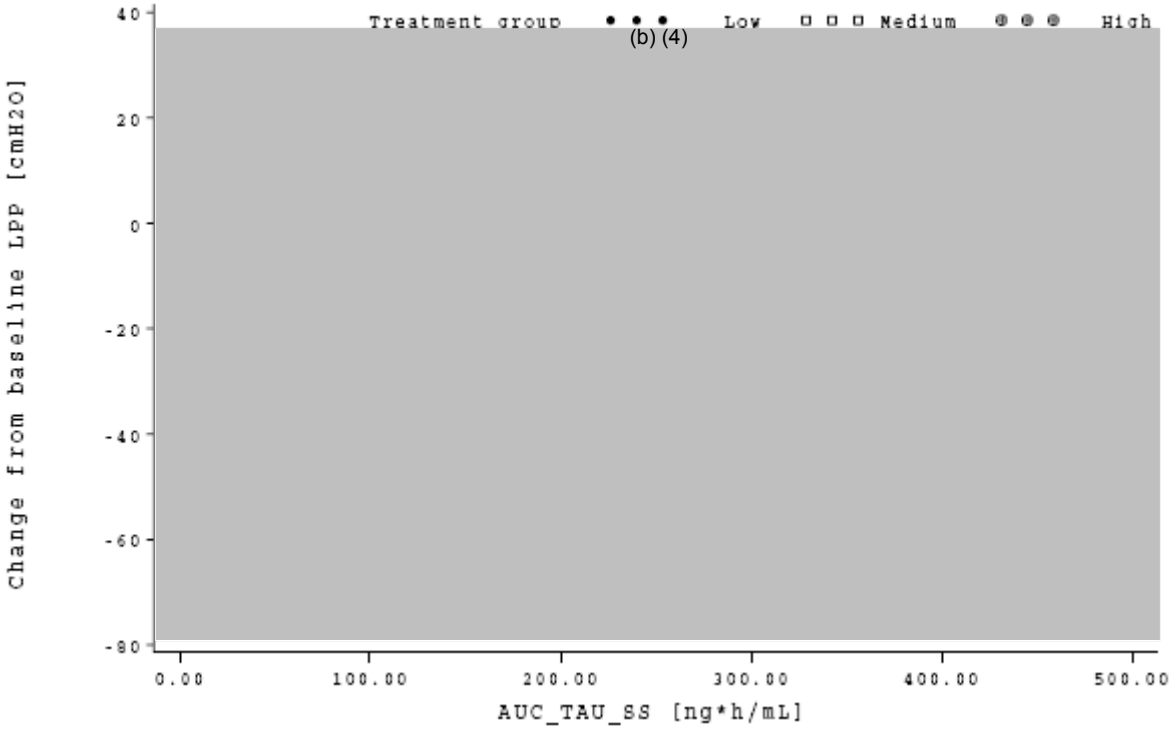
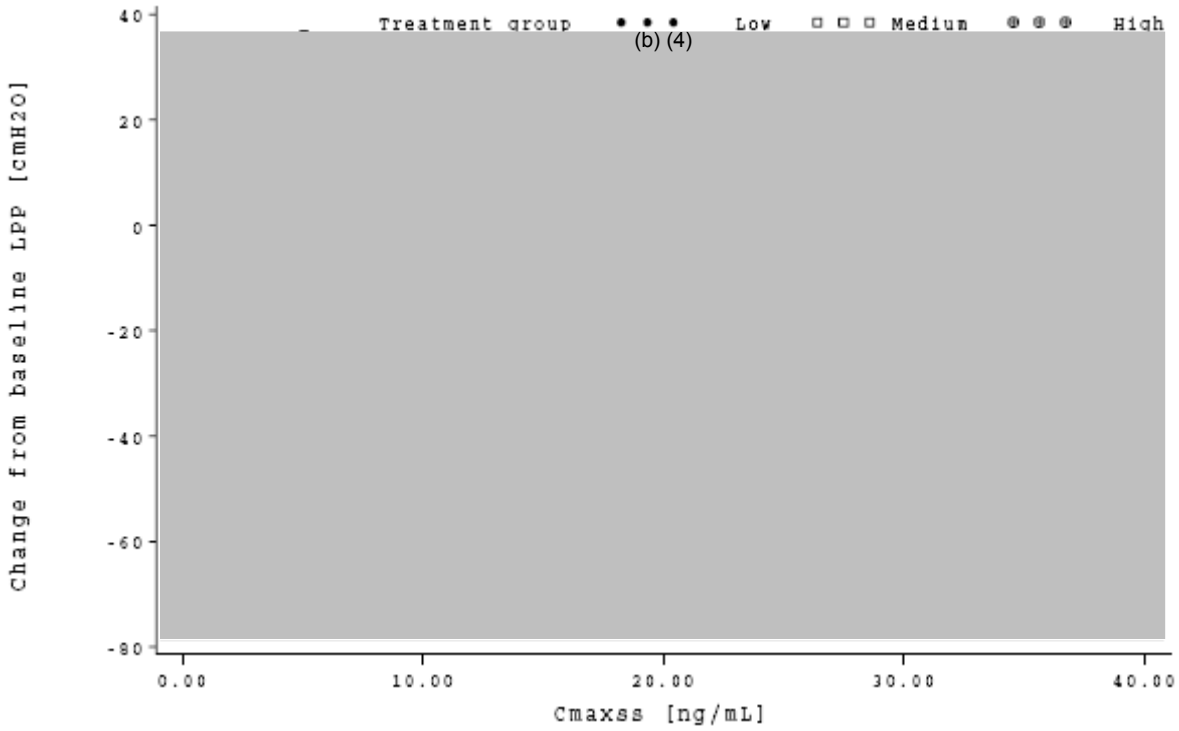


Figure A-8: PK/PD: Relationship between $C_{max\ ss}$ and Detrusor LPP



The relationship between PK parameters and each covariate was investigated. Covariate analysis revealed that body weight and alpha-1 acid glycoprotein (AAG) had effects on both clearance and volume of distribution. No other intrinsic factors including gender, race, population (healthy subjects

vs. patients) or extrinsic factors (co-medication of anti-cholinergic) showed significant effect on PK. Dose-normalized observed concentration vs. body weight profile showed that the pediatric PK is significantly affected by body weight especially for the younger population (outliers with higher concentrations < 40 kg) even with weight-based dose adjustment in these populations. Please refer to Dr. Jee Eun Lee's Pharmacometrics review for details of the pop PK analysis.

SAFETY RESULTS

Among the 30 patients in the Treated set, 14 patients (46.7%) reported at least one AE during the active treatment period. Most of the adverse events occurred while patients were actually taking the low or medium dose level. The most commonly reported adverse events in the study were: urinary tract infection, vomiting, rash, and pyrexia. Aside from pyrexia, all the other adverse events are relatively consistent in nature with the AEs described in the tamsulosin HCl Product Insert (i.e., Flomax®). Most of the adverse events were assessed as either mild or moderate. Two adverse events (ventriculoperitoneal shunt malfunction and urinary tract infection) were assessed as being severe and were not considered to be drug related by the study investigators. Two patients experienced an asymptomatic orthostatic hypotension event. Both of these clinically significant events were considered, by the study investigator, as being related to the study drug. One serious adverse event (ventriculoperitoneal shunt malfunction) was reported and was not considered to be related to study medication by the study investigator. Overall, there were no clinically relevant changes from baseline with the urine or pregnancy dipsticks results. Although there were a few notable findings (e.g., two asymptomatic orthostatic hypotension events mentioned above) and limited sample sizes of the dose groups, none of the vital signs were felt to be of clinical by the study investigator.

CONCLUSION

PK in pediatric population with neurogenic bladders has been adequately characterized. The PK for neurogenic patients were found to be similar to adults when the dosing is adjusted for body weight. No clear relationship was observed between PK parameters and PD parameters after two weeks of treatment at the randomized dose level. Tamsulosin was well tolerated at all weight and dose levels. There are no safety concerns with continued treatment with tamsulosin HCl.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key question.

What is the characteristics of tamsulosin pharmacokinetics in the pediatric population?

The sponsor failed to establish tamsulosin efficacy in pediatric patients. The data were obtained from both healthy pediatric population and the pediatric patients with neuropathic bladder. When weight-adjusted dose (0.2 mg for subjects with 25.1 kg-50 kg and 0.1 mg for subjects with 12.1 kg – 25 kg) was given to the pediatric population, a comparable exposure to that in adults (56.5%-133% of median AUC in adults, 46.3%-119% of median Cmax in adults) was achieved.

2 PERTINENT REGULATORY BACKGROUND

This submission is a labeling supplemental NDA (sNDA) to the Flomax (tamsulosin HCL) NDA 22-579, based on a formal written request (WR) sent to the sponsor pertaining to development of pediatric information for the drug. This labeling sNDA is intended to provide descriptive PK in pediatrics with or without neuropathic bladder and to identify clinically relevant covariates for this population. However, the sponsor failed to establish efficacy from the two trials with pediatric patients with neuropathic bladder.

3 RESULTS OF SPONSOR'S ANALYSIS

The objectives of the population analysis were to describe the pharmacokinetics in pediatric patients with or without neuropathic bladder and to identify clinical relevant covariates for this patient population. Furthermore, it intended to support dosing recommendations for pediatric patients with neuropathic bladder. Single dose PK data obtained from non-neurogenic pediatric patients (Study 527.49) and steady-state PK data from neurogenic pediatric patients (Study 527.66), which included rich sampling, were utilized in developing base structure model. Then sparse sampling data obtained from pediatric patients with neurologic deficit (Study 527.51) were added to the dataset for the final population analysis. The summary of the data from the three trials are described in Table 1. The final model based on those combined data was used to provide the basis for dosing of pediatric patients with neuropathic bladder. Total of 1082 measurements from 189 patients were included in the analysis dataset.

Table 1. Summary of Data for Population Analysis (Source: Table 8.1:4)

Trial No	527.49	527.66	527.51
Design	Open label, Single dose, Parallel group	Open label, Up-titration	Double-blind, Placebo-controlled, Up-titration, Dose ranging

Dose	0.1, 0.2, 0.4, 0.8 mg	Weight-based dose (low, medium, high)	Weight-based dose (low, medium, high)
Stratification	Weight, gender	Weight	Age, anti-cholinergic treatment
Pediatric population	Non-neurogenic	Neurogenic	Neurogenic
Number of Subjects (Male/Female)	45 (22/ 23)	29 (16/13)	115 (67/48)
Age (yr)	10.0 (5-16)	8.0 (2-15)	8.2 (2-16)
Weight (kg)	41.0 (21.8-89.5)	31.6 (12.1-92.2)	27.3 (12.5-71.7)
PK measurements	438	272	417
Sampling points (hr)	Pre, 1, 3, 4, 5, 6, 8, 10, 24, 26	First dose (optional): Pre, 2, 4, 6, 8 Multiple dose: Pre, 2, 4, 6, 8, 10, 24, 33	Visit 5: Pre, >2 h after trough sample Visit 6: > 6 h after dose > 2 h after 6 h sample

One compartment with first order absorption with lag time showed a good agreement with the combined data from all three studies. Covariate analysis revealed that body weight and alpha-1 acid glycoprotein (AAG) had effects on both clearance and volume of distribution, and no other intrinsic factors including gender, race, population (healthy subjects vs. patients) or extrinsic factors (co-medication of anti-cholinergic) showed significant effect on PK. The parameter estimates from the final model is summarized in Table 2.

Dose-normalized observed concentration vs. body weight profile (Figure 1) showed that the pediatric PK is significantly affected by body weight especially for the younger population (outliers with higher concentrations <40kg) even with weight-based dose adjustment in those populations.

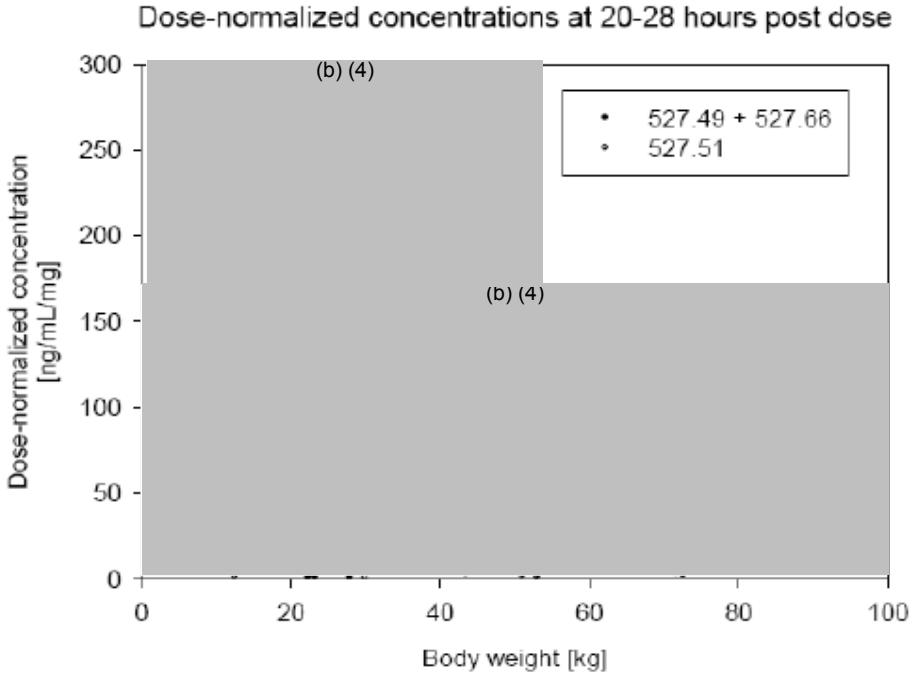


Figure 1. Dose-normalized concentration (20-80 hours post dose) vs. body weight (Source: Figure 15.2.5:1)

Table 2. Final Model and Parameter Estimates from the Final Model (Source: Table 10.1.3.1:1)

Structural Model
$CL/F=\theta_{CL}*(WT/70)^{0.75}*(AAG/20.0)^{\theta_{AAG\_CL}}*e^{\eta_{CL}}$
$V/F=\theta_{V}*(WT/70)*(AAG/20.0)^{\theta_{AAG\_V}}*e^{\eta_{V}}$
$KA=\theta_{KA}*e^{\eta_{KA}}$
$ALAG1=\theta_{ALAG1}$
Residual Random Effect Model
$Y=\hat{Y}*(1+\varepsilon_1)+\varepsilon_2$

Parameter	Estimate	SE(%)	Description
CL/F (L/hr)	2.28	4.21	Apparent clearance
θ_{AAG_CL}	-0.844	-15.1*	The effect of AAG on the apparent clearance
V/F (L)	37.5	6.35	Apparent volume of distribution of central compartment
θ_{AAG_V}	-0.663	-24.3*	The effect of AAG on the apparent volume of distribution
KA (/hr)	0.368	12.0	First order absorption rate constant
ALAG1 (hr)	0.957	1.14	Absorption lag time
IIV in CL/F (CV%)	54.4	11.4	Inter-individual variability in the apparent clearance
IIV in V/F (CV%)	61.2	17.7	Inter-individual variability in the volume of distribution
IIV in KA (CV%)	117	19.7	Inter-individual variability in the first order absorption rate constant
Cov_V/CL	0.238	16.7	Covariance between inter-individual variability in the apparent clearance and inter-individual variability in the apparent volume of distribution. The estimate translates to a coefficient of correlation of 0.715
Proportional residual variability (CV%)	28.4	6.13	
Additive residual variability (SD ng/mL)	0.178	27.0	

* The sponsor reported negative values by taking negative estimates rather than the absolute value of the estimates for the relative standard error calculation.

A.2. Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	20-579 / S-026	**Brand Name**	Flomax
OCP Division	DCP3	**Generic Name**	Tamsulosin HCl
Medical Division	DRUP	**Drug Class**	Antagonist of alpha1A adrenoceptors in the prostate
OCP Reviewer	Chongwoo Yu, Ph.D	**Indication(s)**	Treatment for pediatric patients 2-16 years of age with elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida)
OCP Team Leader	Myong Jin Kim, Pharm. D.	**Dosage Form**	Capsules
Secondary Reviewer	Myong Jin Kim, Pharm.D.	**Dosing Regimen**	Once daily
Date of Submission	June 25, 2009	**Route of Administration**	Oral
Estimated Due Date of OCP Review	October 25, 2009	**Sponsor**	Boehringer Ingelheim Pharmaceuticals
PDUFA Due Date	December 23, 2009	**Priority Classification**	Priority
Division Due Date	November 25, 2009		

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	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		527.66
Phase 3 clinical trial:	X	1		527.51
Population Analyses -				
PK:	X			
PD:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Literature References				
Total Number of Studies				

Other comments

	Comments
QBR questions (key issues to be considered)	1. Acceptability of proposed labeling. 2. PK/PD analyses. 3. Population PK analyses for effect of covariates.. 4. Sufficient bioanalytical assay validation information? 5. Acceptability of the proposed PLR label
Other comments or information not included above	

Filing Memo

Clinical Pharmacology Review

NDA: 20-579 / S-026
Compound: Flomax (tamsulosin HCl) capsules 0.4 mg
Sponsor: Boehringer Ingelheim

Date: 7/29/2009
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Tamsulosin hydrochloride (HCl) has been developed as a modified-release capsule for the treatment of BPH (Benign prostatic hyperplasia) in adults and was registered in the US for this indication under NDA 20-579 on April 15, 1997. Tamsulosin HCI is available as Flomax® 0.4 mg capsules.

A formal Written Request (WR) was sent to Boehringer Ingelheim Pharmaceuticals, Inc. on January 10, 2006 pertaining to the development of pediatric information for tamsulosin HCl. Three formal amendments to the original WR were made dated March 20, 2006, October 18, 2006, and May 3, 2007. The initial WR and subsequent three formal amendments outline a specific and agreed upon development plan. It consists of two clinical trials, designated as Study 1 (Study 527.66) and Study 2 (Study 527.51), which were intended to characterize the use of tamsulosin HCl as treatment for pediatric patients 2-16 years of age with elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida). The agreed upon timeframe for submitting reports from these studies to the Agency was on or before July 1, 2009.

This complete response to the tamsulosin HCI Written Request is being submitted as a labeling supplemental new drug application (sNDA) with clinical data (SE-8) to the Flomax® NDA 20-579. This labeling sNDA is intended to support two objectives. The first is to provide complete information and appropriate proposed pediatric labeling in response to the Written Request. The second objective is to take the opportunity and reformat the Flomax® package insert in order to establish compliance with the Physician's Label Rule (21 CFR 201.57).

Formulation:
Tamsulosin HCl Capsules, 0.025 mg, 0.1 mg and 0.2 mg were developed to provide an age-appropriate formulation for the pediatric population. The capsules were formulated for US pediatric program as (b) (4)

(b) (4)

(b) (4) Dosing of the investigational pediatric capsules was accomplished by opening the capsules and sprinkling the contents in an appropriate soft food (e.g., applesauce).

The pediatric program was designed to include multi-national studies; therefore, it was necessary to use an alternate formulation of tamsulosin capsules in some participating countries. The alternate formulation is approved under the trademark of Omnic® in Europe and is identical to Flomax® with the exception of a small amount of the excipient, calcium stearate, which is used as (b) (4) A BE study (study ARI10021, submitted under NDA 21-319/S-014, approved on June 19, 2008) comparing Omnic® 0.4 mg and Flomax® 0.4 mg under fasting condition showed that they are bioequivalent (a review on this study can be found in Dr. Donny Tran's review dated April 17, 2008 under NDA 21-319/S-014 available in DFS).

(b) (4)

(b) (4) Details on formulation development of active and placebo

clinical capsules were provided in an IND Amendment dated April 4, 2006 (IND 30,365, Serial No. 0262). This amendment also provided information regarding the effect of mixing the granules with applesauce on drug release. This was assessed by comparing the dissolution profile of the tamsulosin HCl intact capsules, granules alone and granules in applesauce. Dissolution data will be reviewed by CMC.

Clinical Pharmacology:
The Pharmacokinetics (PK) of tamsulosin HCl in adults has been well characterized. The two clinical trials in the WR were conducted to characterize the clinical pharmacology of tamsulosin HCl in pediatric patients. Phase 2, Study 527.66 in neurogenic patients was conducted to characterize the PK/Pharmacodynamics (PD) profile, and Phase 2b/3, Study 527.51 in neurogenic patients with sparse PK sampling was a dose ranging study to evaluate the safety and efficacy of a range of doses (low, medium, high) of tamsulosin as treatment in children.

Population PK (pop PK) analysis was conducted to describe the PK in pediatrics with or without neuropathic bladder and to identify clinical relevant covariates for this patient population. In addition, pop PK analysis was used to support dosing recommendation for pediatric patients with neuropathic bladder.

Labeling:
In accordance to the WR the proposed indication was "treatment of pediatric patients 2-16 years of age with elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida)." Upon completion and analysis of the results from the safety and efficacy trial (Written Request Study 2) it was determined by the Sponsor that efficacy in the targeted pediatric population could not be supported. Subsequently, the participation from ongoing patients who rolled over into Study 1 (from Study 2) was terminated by the Sponsor for ethical considerations (i.e., the benefit/risk assessment became unfavorable). Upon termination of Study 1, the patient numbers delineated within the WR had already been obtained.

The FDA was informed on April 15, 2009 (Serial No. 0288) of both the Study 527.66 termination as well as the Sponsor's conclusion that the planned indication could not be supported, as per the results of Study 527.51. While the efficacy results from Study 527.51 do not support the pursuit of a formal indication, the Sponsor is proposing to include additional text within the label Section 8.4 entitled "Special Populations: Pediatric Population." The proposed text briefly outlines the two studies that were performed in the targeted pediatric population and presents both the conclusion that efficacy had not been established as well as the most frequent adverse events observed in the trials. The Sponsor does not propose to present any PK/PD study results in the label.

Marketing Exclusivity:
Sponsor believes that they have satisfactorily met the full terms of the January 10, 2006 WR with regard to both the content and timeline commitments. The Sponsor is requesting that the pediatric exclusivity be granted to this NDA with accompanying additional 6 month market exclusivity.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 20-579 / S-026 is fileable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20579	SUPPL-26	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLOMAX (TAMSULOSIN HCL) 0.4MG CAPSULES

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

/s/

CHONGWOO YU
12/01/2009

JEE E LEE
12/02/2009

PRAVIN R JADHAV
12/02/2009

MYONG JIN KIM
12/03/2009