CLINICAL REVIEW

Application Type	sNDA
Submission Number	20-579/S-026
Submission Code	SE8
Letter Date	June 25, 2009
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Reviewer Name	Chong M. Kim, M.D., Ph.D.
Review Completion Date	November 25, 2009
Established Name	tamsulosin HCl
Trade Name	Flomax®
Therapeutic Class	alpha adrenergic antagonist
Applicant	Boehringer Ingelheim
Priority Designation	P
Formulation	0.4 mg capsules
Dosing Regimen	once daily
Indication	Reduction in Detrusor Leak Point Pressure
Intended Population	Children age 2-16 years old

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Pivotal trial BI 527.51 does not support the efficacy of daily dosing of oral tamsulosin HCl for the reduction in detrusor leak point pressure in children age 2-16. There were no new safety signals in this application. With minor modification, the Sponsor's inclusion of the negative new study data into the current PI is acceptable. Therefore, despite the study not showing efficacy, this application is recommended for approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

For treatment of the signs and symptoms of BPH, tamsulosin HCl is marketed as Flomax® within the United States. For this application, tamsulosin HCl use was studied to prevent renal function deterioration in children with neuropathic bladders by decreasing the detrusor leak point pressure. It would have been administered to children as an oral medication.

1.3.2 Efficacy

Trial BI 527.51 was a randomized, multi-center, double-blinded, placebo-controlled, parallel-group study to determine the efficacy and safety of oral tamsulosin in the reduction of detrusor

leak point pressure. This single pivotal trial compared the efficacy and safety of oral tamsulosin, 0.025 mg to 0.4 mg (based on weight), to placebo in the reduction of detrusor leak point pressure in children with neuropathic bladders. This multinational Phase III study was conducted in the Americas, Asia, and Europe. A total of 161 patients randomized into the study received at least one dose of study medication and are included in the intent-to-treat and safety populations.

The primary efficacy endpoint was response to treatment defined as patients who decreased their detrusor leak point pressure (LPP) based upon two evaluations on the same day to less than 40 cm H_20 at Week 14 (end of treatment). Of the 161 patients treated (FAS-LPP), there were 30 in the 2 to <5 years age group, 70 in the 5 to <10 years age group, and 61 in the 10 to 16 years age group. The proportions of responders in each tamsulosin HCl dose group and the placebo group were compared for the FAS- LPP dataset.

- A total of 135 patients were included in the primary analysis and showed a 37.8% overall response rate. The response rates for the placebo, low, medium and high tamsulosin dose groups were 35.3%, 45.7% (p=0.54), 27.3% (p=0.34) and 42.4% (p=0.52), respectively. Adjusting for age group, anti-cholinergic use at baseline, and geographic region, the proportion of responders in each of the dose groups was not statistically significantly different from that of the placebo group.
- The same analysis was performed for PPS-LPP, which excluded patients with important protocol violations which might have impacted patients' response to treatment. There were 115 patients included in this analysis with an overall response rate of 40.0%. The pattern of the individual response rates for the four treatment groups was very similar as that for the FAS-LPP. No statistically significant difference was found between the proportions of responders in any of the tamsulosin dose and the placebo dose groups.

1.3.3 Safety

The mean exposure to study medication was 99.4 days (approximately 14 weeks). The number of patients exposed to study medication for >99 days was balanced across the four treatment groups: 33 (80.5%) on placebo, 31 (77.5%) on low dose, 34 (87.2%) on medium dose, and 35 (85.4%) on high dose tamsulosin HCl.

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. They included regular assessments of vital signs, orthostatic testing, physical exam, ECGs, vision, cognitive testing, and monitoring of hematology, blood chemistry, and urine.

Of the 161 patients who received at least one dose of study treatment, the frequency of overall AEs was 39 (32.5%) for low dose, 24 (30.0%) for medium dose, 15 (37.5%) for high dose group, and 18 (43.9%) in the placebo group. The most frequently reported AEs in the treatment groups (placebo vs tamsulosin), were urinary tract infection (9.8% vs 11.7%), vomiting (12.2% vs 7.5%), nasopharyngitis (2.4% vs 9.2%), headache (14.6% vs 4.2%), influenza (7.3% vs 5.0%),

and abdominal pain (14.6% vs 1.7%). Drug-related AEs were reported in nine patients: two in the placebo group, four in the tamsulosin HCl low dose group, one in the medium dose group, and two in the high dose group.

Four patients experienced one or more serious adverse events (SAEs) during the treatment phase of the study (two in the placebo group, one in the tamsulosin HCl low dose group, and one in the medium dose group). The patient receiving low dose tamsulosin HCl died of indeterminate causes. Two patients (not including the patient who died) were discontinued from the study prematurely due to AE(s) (Patients 5323 and 5281). The case narratives of the above AEs were reviewed and are not considered related to study medication. The case narrative of the one death report was inconclusive due to lack of information.

1.3.4 Dosing Regimen and Administration

The effects of demographic variables, such as body weight and age, on pharmacokinetics were considered clinically significant. Patients were thus stratified by age and treatment arms were divided into low, medium, and high dose groups. Even within the low, medium and high dose groups, dosing was based on weight, as shown in the Table below:

Weight (kg)	tamsulosin HCl Low dose (0.001 – 0.002 mg/kg)	tamsulosin HCl Medium dose (0.002 – 0.004 mg/kg)	tamsulosin HCl High dose (0.004 – 0.008 mg/kg)	Placebo
12.5 – 25.0	0.025 mg	0.05 mg	0.1 mg	x
25.1 – 50.0	0.05 mg	0.1 mg	0.2 mg	x
50.1 – 100.0	0.1 mg	0.2 mg	0.4 mg	x

The sponsor utilized a staged titration process for dosing tamsulosin HCl in children. Patients randomized to medium and high dose tamsulosin HCl were required to begin treatment with the low dose prior to titrating to their randomized dose. Thus, the highest number of these patients were exposed to the low dose (n = 120), followed by the medium dose (n = 80), and then the high dose (n = 40) of tamsulosin HCl.

1.3.5 Drug-Drug Interactions

No new drug interaction studies were submitted in this application. Tamsulosin is primarily metabolized via CYP3A4 and CYP2D6 enzyme system. It is affected by concomitant strong CYP inhibitors. Concomitant administration of ketoconazole 400 mg once daily for 5 days and a single dose of tamsulosin 0.4 mg on the 4th day caused a 2.2 fold increase in tamsulosin C_{max} and a 2.8 fold increase in tamsulosin AUC. Concomitant administration of paroxetine 20 mg once daily for 9 days and a single dose of tamsulosin 0.4 mg on the 8th day caused a 1.3 fold increase in tamsulosin C_{max} and a 1.6 fold increase in tamsulosin AUC.

1.3.6 Special Populations

The patients in this study were children aged between two and 16 years, with elevated detrusor leak point pressure associated with a known neurologic defect (e.g., spina bifida).

The study patients were 2-16 years of age and represent 3 separate strata based on age. Of the 161 patients treated (FAS-LPP), there were 30 randomized into the 2 to <5 years age group, 70 randomized into the 5 to <10 years age group, and 61 randomized into the 10 to 16 years age group. Completion rates for study medication were similar across the age groups: 97% in the 2 to <5 age group, 91% in the 5 to <10 age group, and 90% in the 10 to 16 age group.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Tamsulosin HCl (Flomax®) is an alpha$_1$ adrenergic receptor antagonist and was approved by the Agency in 1997 under NDA 20-579 for treatment of the signs and symptoms of Benign Prostatic Hyperplasia (BPH).

The recommended tamsulosin oral dose for the treatment of signs and symptoms of BPH is 0.4 mg. For those patients who fail to respond to the 0.4 mg dose after two to four weeks of dosing, the dose of Flomax can be increased to 0.8 mg once daily.

The time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when tamsulosin capsules are administered with food. Taking tamsulosin capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions. Flomax is extensively bound to plasma proteins, primarily alpha-acid glycoprotein (AAG). However, *in vitro* studies indicate that the binding of tamsulosin hydrochloride to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin hydrochloride had no effect on the extent of binding of these drugs.

Tamsulosin is primarily metabolized via CYP3A4 and CYP2D6 enzyme system. It is affected by concomitant strong CYP inhibitors. Concomitant administration of ketoconazole 400 mg once daily for 5 days and a single dose of tamsulosin 0.4 mg on the 4th day caused a 2.2 fold increase in tamsulosin C_{max} and a 2.8 fold increase in tamsulosin AUC. Concomitant administration of paroxetine 20 mg once daily for 9 days and a single dose of tamsulosin 0.4 mg on the 8th day caused a 1.3 fold increase in tamsulosin C_{max} and a 1.6 fold increase in tamsulosin AUC.

For this application, tamsulosin use is proposed to prevent renal function deterioration in children with neuropathic bladders by decreasing the detrusor leak point pressure. It will be administered as an oral medication. The effects of demographic variables, such as body weight and age, on pharmacokinetics were considered clinically significant. Patients were thus stratified by age and treatment arms were divided into low, medium, and high dose groups. Within these 3 dose groups, the individual dosing was based on weight.

2.2 Currently Available Treatment for Indications

There are no drug products currently approved for the sponsor's proposed indication of Reduction of Detrusor Leak Point Pressure in children with neuropathic bladders.

2.3 Availability of Proposed Active Ingredient in the United States

Tamsulosin HCl is currently approved under NDA 20-579 for treatment of the signs and symptoms of Benign Prostatic Hyperplasia (BPH).

2.4 Important Issues With Pharmacologically Related Products

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in FLOMAX capsule-treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope. Such information appears in the label for tamsulosin HCl.

2.5 Presubmission Regulatory Activity

NDA 20-579 was approved for once daily oral dosing of tamsulosin HCl for treatment of the signs and symptoms of Benign Prostatic Hyperplasia in 1997 under the trade name Flomax.

An initial tamsulosin pediatric Written Request was issued on January 10, 2006. The Indication to be pursued was "the 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)." The tamsulosin HCl Written Request was formally amended on three separate occasions. The first amendment was on 20 March 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 18 October 2006 and specified that Day 1 pharmacokinetics could be characterized in at least 9 patients (rather than all patients) who were reasonably distributed across three body weight ranges of Study 1 (527.66). The third and final amendment to the Written Request was on 03 May 2007 and included the important agreement that the Written Request PK/PD Study could continue and the Pivotal Efficacy Study could be initiated in advance of DRUP completing the review of the initial PK/PD Study.

This complete response to the tamsulosin HCl Written Request is being submitted as a labeling supplemental new drug application (sNDA) to the FLOMAX NDA 20-579. This sNDA is intended to provide complete information and appropriate pediatric labeling in response to the Written Request.

2.6 Other Relevant Background Information

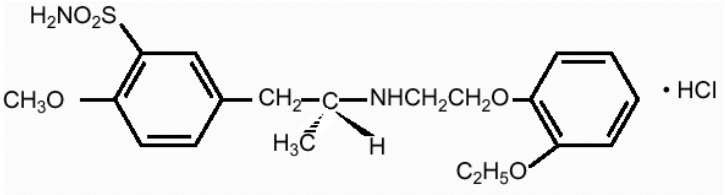
During the discussions held in advance of the tamsulosin HCl Written Request it was agreed that the requirement for a pediatric formulation would be satisfied by the continued commercialization of the current 0.4 mg capsule and introduction of newly developed 0.025 mg, 0.1 mg, and 0.2 mg capsules. (b) (4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Tamsulosin hydrochloride is (-)-(*R*)-5-[2-[[2-(*o*-Ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin hydrochloride 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 hydrochloride is $C_{20}H_{28}N_2O_5S \bullet HCl$. The molecular weight of tamsulosin hydrochloride is 444.98. Its structural formula is:



Each FLOMAX capsule for oral administration contains tamsulosin hydrochloride 0.4 mg, and the following inactive ingredients: methacrylic acid copolymer dispersion NF, microcrystalline cellulose, triacetin, calcium stearate, talc, FD&C blue No. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts of black edible ink.

In discussions that preceded the Written Request, it was agreed that tamsulosin could be administered to pediatric patients in the clinical trials as "sprinkles" (opening the capsule and sprinkling out the beads) in applesauce or yogurt. Stability testing confirmed that this was acceptable if sprinkling occurred shortly before ingestion of the sprinkled food. Discussions also focused on the use of Omnic, the European version of Flomax, in these trials. Based upon acceptable dissolution testing showing no significant differences, the use of Omnic was permitted in the pediatric trials. The reader is referred to the Chemist's review.

3.2 Animal Pharmacology/Toxicology

The principal pharmacologic action of Tamsulosin hydrochloride is that of an antagonist of $alpha_{1A}$ adrenergic receptors in the prostate. At least three discrete $alpha_1$-adrenergic receptor subtypes have been identified: $alpha_{1A}$, $alpha_{1B}$ and $alpha_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the $alpha_1$-receptors in human prostate are of the $alpha_{1A}$ subtype.

The dynamic component of BPH is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of $alpha_1$ adrenergic receptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenergic receptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.

In discussions that preceded the Written Request, the Sponsor agreed to conduct a juvenile monkey study to assess any new potential risks in a juvenile animal model. There was discussion of potential affects on serum prolactin and estradiol. This study was eventually conducted by Sponsor and showed no clinically meaningful affects on serum hormones and no new signals in the juvenile model. The reader is referred to the Pharmacologist's review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

26-July-2009-Original submission of the clinical study report for the pivotal, Phase 3, efficacy Study BI 527.51

26-July-2009- Original submission of the clinical study report for the PK/PD and extended safety Study BI 527.66

4.2 Table of Clinical Studies

Study Number	Protocol Title	First Patient In	Last Patient Out
527.51	A phase IIB/III, multicenter, DB, randomised PC, dose ranging study of tamsulosin hydrochloride (low, medium or high dose) as treatment in children with neuropathic bladder for 3 months.	05-NOV-2007	12-FEB-2009
527.66	An uncontrolled, open-label, titration, long-term safety (up to 12 months) and efficacy study of tamsulosin hydrocloride in children with neuropathic bladder, with a randomized pharmacokinetic sub-study investigating low, medium, and high dose ranges.	19-APR-2006	

4.3 Review Strategy

This medical reviewer independently reviewed pivotal trial BI 527.51 for safety and efficacy and the uncontrolled extended open-label study BI 527.66 for safety. The Clinical and Biometrics teams collaborated on their independent findings before making final recommendations.

4.4 Data Quality and Integrity

DSI consult was not requested.

4.5 Compliance with Good Clinical Practices

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

DISPOSITION OF PATIENTS IN STUDY BI 527.51:
Overall, there were 231 patients enrolled in this clinical study; 162 patients met eligibility criteria and were randomized to one of the four treatment groups, with 161 patients receiving at least one dose of study drug. Of the 161 patients treated, there were 30 in the 2 to <5 years age group, 70 in the 5 to <10 years age group, and 61 in the 10 to 16 years age group.

Of the 161 patients who received at least one dose of study treatment, 148 (91.9%) patients completed the 14-week treatment regimen. Medication completion rates for each dosing group ranged from 87.8% (36/41) for patients in the placebo group to 97.6% (40/41) for patients in the tamsulosin HCl high dose group.

Of the 13 (8.1%) patients that did not complete 14 weeks of trial medication, five were lost to follow-up, three discontinued due to an AE, two were not compliant with the protocol, two withdrew consent, and one was classified as "other" due to issues with study visit scheduling.

Table 1. Patient disposition and trial medication completion by treatment group

		Tamsulosin Dose Groups			
	Placebo	Low	Medium	High	Total
Enrolled					231
Randomised					162*
Not treated	0	0	1	0	1
Treated, N	41	40	39	41	161
Did not prematurely discont. trial med. N (%)	36 (87.8)	36 (90.0)	36 (92.3)	40 (97.6)	148 (91.9)
Prematurely discontinued from trial med. N (%)	5 (12.2)	4 (10.0)	3 (7.7)	1 (2.4)	13 (8.1)
AE (unexpected worsening of disease under study)	0	0	0	0	0
AE (unexpected worsening of pre-existing disease)	0	0	0	0	0
AE other	1 (2.4)	2 (5.0)	0	0	3 (1.9)
Non compl. protocol	0	0	2 (5.1)	0	2 (1.2)
Lost to follow-up	2 (4.9)	2 (5.0)	1 (2.6)	0	5 (3.1)
Consent withdrawn, not due to AE	1 (2.4)	0	0	1 (2.4)	2 (1.2)
Other	1 (2.4)	0	0	0	1 (0.6)

* Patient 5007 was randomised to medium dose tamsulosin HCl, but withdrew consent prior to receiving treatment.
Source: Table 15.1.1: 3

PROTOCOL VIOLATIONS IN STUDY BI 527.51:
Of the 161 treated patients, 36 (22.4%) patients had at least one potentially important protocol violation during the clinical study, for a total of 38 occurrences. Overall, the most frequent important protocol violations were: patient with <2 LPP evaluations performed at end of treatment (16 patients), taking medication for unstable bladder (7 patients), and food not ingested before first dose or PK sampling (7 patients). Across the four treatment groups, the numbers of patients with protocol violations were well balanced, ranging from 8 to 11.

Table 2. Protocol violations, Treated Set

		Tamsulosin Dose Groups			
	Placebo	Low	Medium	High	Total
Number of patients, N	41	40	39	41	161
Number of patients with at least one important protocol violation, N	8	11	9	8	36
Total occurrences of important PV, N (%)	8	11	10	9	38
Patient had < 2 LPP evaluations performed at end of treatment	3 (37.5)	6 (54.5)	1 (10.0)	6 (66.7)	16 (42.1)
Patient's bladder therapy not stable	1 (12.5)	1 (9.1)	3 (30.0)	2 (22.2)	7 (18.4)
Patient's meal/snack not ingested before first dose of study med or PK sampling	2 (25.0)	2 (18.2)	2 (20.0)	1 (11.1)	7 (18.4)
Informed consent given late, after screening visit or after D/C of excluded meds	0	2 (18.2)	2 (20.0)	0	4 (10.5)
Patient spits out applesauce or yogurt w/study med or vomits with 1st hour post/drug	1 (12.5)	0	1 (10.0)	0	2 (5.3)
Child assent not given	0	0	1 (10.0)	0	1 (2.6)
Patient had decrease in systolic BP in orthostatic test 20 mm Hg or more & not discontinued	1 (12.5)	0	0	0	1 (2.6)

Source: Table 15.1.2: 1

PROTOCOL AMENDMENTS
One protocol amendment dated 25-Sept-2007 was submitted to the original protocol and was implemented prior to the completion of the study (12-Feb-2009). None of the changes affected the integrity of the analyses of the primary endpoints. The changes included clarification of inclusion/exclusion criteria and limitation of number of venipunctures allowed for PK assessment.

4.6 Financial Disclosures

All of the clinical investigators, from both the US and non-US sites, responded and none had any relevant financial disclosure information to declare. Therefore, there is no reason to suspect that the results of the pivotal trial BI 527.51 were compromised due to financial arrangements between the sponsor and the clinical investigators

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics/ADME

Absorption of tamsulosin hydrochloride from FLOMAX capsules 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin hydrochloride exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing. The time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when FLOMAX capsules are administered with food. Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin hydrochloride in plasma range from five to seven hours. Because of absorption rate-controlled pharmacokinetics with Flomax® (tamsulosin hydrochloride) capsules, the apparent half-life of tamsulosin hydrochloride is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target adult population.

Tamsulosin hydrochloride is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. *In vitro* results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug metabolizing enzymes may lead to increased exposure to tamsulosin. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Tamsulosin hydrochloride is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way *in vitro* studies indicate that the binding of tamsulosin hydrochloride to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin hydrochloride had no effect on the extent of binding of these drugs.

5.2 Pharmacodynamics

The urological pharmacodynamics in adult males with BPH (e.g., maximum urinary flow rate), are well described in the product labeling. The urodynamic findings from the studies in pediatric patients are described in the next sections of this review.

5.3 Exposure-Response Relationships

Two different formulations of study drug were used during the trial. They were referred to as the US FLOMAX and EU OMNIC formulations (mainly as US and EU formulations). Both the US and EU formulations are identical in component composition except for a minor

difference in the amount of calcium stearate. Ultimately, both Clinical Pharmacology and Chemistry found the use of both Omnic and Flomax to be acceptable.

The sponsor studied multiple doses for treatment groups labeled as low, medium, and high dose in this pivotal Phase 3 study. The daily dose in each dosing category was calculated based on body weight. Daily tamsulosin HCl doses were either 0.025, 0.05, 0.1, 0.2, or 0.4 mg, supplied as a modified release, non-branded capsules and matching placebo capsules from (b) (4) All patients received their randomized dose (either active medication or placebo) via opened capsules with the combined contents sprinkled over a single teaspoonful (5 mL) of applesauce or yogurt. This method of administration was found acceptable by both Clinical and Clinical Pharmacology.

Table 3. Dosing scheme.

Weight (kg)	tamsulosin HCl Low dose (0.001 – 0.002 mg/kg)	tamsulosin HCl Medium dose (0.002 – 0.004 mg/kg)	tamsulosin HCl High dose (0.004 – 0.008 mg/kg)	Placebo
12.5 – 25.0	0.025 mg	0.05 mg	0.1 mg	x
25.1 – 50.0	0.05 mg	0.1 mg	0.2 mg	x
50.1 – 100.0	0.1 mg	0.2 mg	0.4 mg	x

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Reduction in detrusor leak point pressure in children age 2-16 with neuropathic bladders.

6.1.1 Methods

The efficacy review was confined to pivotal trial BI 527.51

General Discussion of Endpoints

The primary efficacy variable was the percentage change in patients who decrease their detrusor leak point pressure (LPP) based upon two evaluations on the same day to less than 40 cm H_2O at Week 14. This is considered an acceptable endpoint for this indication based upon its routine use in clinical practice, as well as extensive published literature showing its clinical meaningfulness.

A total of 135 patients were included in the primary analysis and showed a 37.8% overall response rate in the treatment groups. The numbers of patients in the analysis populations are provided in Table 4 below.

Table 4. Number of patients in analysis sets

		Tamsulosin Dose Groups			
Patient Analysis Sets	**Placebo**	**Low**	**Medium**	**High**	**Total**
Entered/Randomised, N	41	40	40	41	162*
Treated set (TS), N	41	40	39	41	161*
Full analysis set (FAS-LPP), N	41	40	39	41	161
FAS-LPP at Week 14	34	35	33	33	135
Per protocol set (PPS-LPP), N	37	33	35	33	138
PPS-LPP at Week 14	30	28	30	27	115
Patient had an important efficacy-related protocol violation	4	7	4	8	23
Renal full analysis set (FAS-RENAL), N	40	38	38	40	156
Patient without an on-treatment renal ultrasound measurement	1	2	1	1	5
Catheterisation FAS-CATH, N	29	21	22	23	95
Patient without catheterisation diary**	11	19	17	18	65
Patient without an on-treatment catheter measurement	1	0	0	0	1

*Patient 5007 was randomised into the study but withdrew consent prior to receiving treatment.
**Only patients on catheterisation therapy completed a catheterisation diary
Source: Table 15.1.3: 1

For the primary endpoint, percentage of patients achieving LPP < 40 cm H_20, the response rates for the placebo, low, medium and high tamsulosin dose groups were 35.3%, 45.7%, 27.3% and 42.4%, respectively. The proportion of responders in each of the dose groups was not statistically significantly different from that of the placebo group and there was no evidence of linear dose-response relationship (see Table 5 below).

Table 5. Response rates by treatment group at Week 14 (FAS-LPP)

		Tamsulosin Dose			
	Placebo	**Low**	**Medium**	**High**	**Total**
Number of Patients	34	35	33	33	135
LPP Responder N (%)	12 (35.3)	16 (45.7)	9 (27.3)	14 (42.4)	51 (37.8)
Odds Ratio 95% CI	--	1.38 (0.50, 3.80)	0.59 (0.20, 1.76)	1.41 (0.50, 3.97)	--
p-value	--	0.5388[1]	0.3430[1]	0.5209[1]	0.9436[2]

[1] Dose group vs. placebo
[2] Cochran-Armitage trend test
Source: Table 15.2.1.2: 1

The same analysis was performed for the primary endpoint in the per-protocol population (referred to as PPS-LPP), which excluded patients with important protocol violations which might have impacted patients' response to treatment. There were 115 patients included in this analysis, with an overall response rate of 40.0%. The pattern of the individual response rates for the four treatment groups was very similar as that for the FAS-LPP. No statistically significant difference was found between the proportions of responders in any of the tamsulosin dose and the placebo dose groups in this analysis.

Logistic regression was also performed with the non-completer considered as failures (NCF) approach for the full analysis set (FAS-LPP). A total of 151 patients were included in this analysis with an overall response rate of 33.8%. The numbers of responders for the placebo, low, medium, and high treatment group were 12 (30.0%), 16 (41.0%), 9 (24.3%) and 14 (40.0%), respectively. There was no statistically significant difference between the proportions of responders in each of the tamsulosin dose groups versus the placebo group in this analysis.

Secondary endpoint:
Change in LPP from baseline to the end of treatment at Week 14 between each dose group and the placebo group was compared for the FAS-LPP. The least squares mean changes from baseline to Week 14 for the placebo, low, medium and high dose group were -11.4, -17.6, -4.6 and -14.3 cm H_2O, respectively. No statistically significant difference in change in LPP from baseline to Week 14 between any dose group and the placebo group was found. The same analysis was performed for PPS-LPP and there was no significant difference in change in LPP from baseline between any of the tamsulosin HCl dose groups and the placebo group (see Table 6 below).

Table 6. Change in LPP from baseline to the end of treatment at Week 14 (FAS-LPP)

	Placebo	Tamsulosin Dose			Total
		Low	Medium	High	
Baseline					
Number of patients	41	40	39	41	161
Mean	58.5	62.6	63.3	57.0	60.3
SD	22.1	20.8	27.0	22.4	23.1
Change from baseline at Week 14					
Number of patients	30	32	31	33	
LSMeans	-11.4	-17.6	-4.6	-14.3	
SE	4.6	4.5	4.4	4.3	
Differences to Placebo					
p-value*		0.3097	0.2676	0.6265	
95% CI		(-18.22, 5.83)	(-5.28, 18.85)	(-14.84, 8.98)	

*ANCOVA model with covariates of age group, anti-cholinergic use at baseline and geographic region
Source: Table 15.2.1.3: 1

6.1.3 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in children 2-16 years of age with neuropathic bladders. The study consisted of a 1-week screening period, a two-week double-blind dose titration period, and a 12-week double-blind maintenance period. The total study duration was approximately 14 weeks.

This Phase III study was conducted in centers in the Americas, Asia, and Europe. A total of 162 patients were randomized to one of the four treatment groups: placebo, low, medium or high dose tamsulosin hydrochloride.

Stratification was defined by the 2 to <5 years age group, 5 to <10 years age group, and 10 to 16 years age group. Patients were also stratified based upon concomitant use of anti-cholinergic medication into two strata, yes or no.

Of the 161 patients who received at least one dose of study treatment, 135 patients completed the 14-week treatment regimen and are included in the intent to treat (full analysis set). The full analysis set (FAS-LPP) was used for analysis of the primary endpoint. The schedule of treatments and procedures is shown in Table 7 below.

Table 7. Schedule of treatments and procedures

Trial Periods	*Screen*	*Dose Titration*			*Maintenance Treatment*		*End of Treat*	*End of Trial*
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**	**8[2]**
Week	**-1**	**0**	**1**	**2**	**6**	**10**	**14**	**18**
Day	**-7 to -1**	**1**	**7 (±1)**	**14 (±1)**	**42 (±3)**	**70 (±3)**	**98 (±3)**	**126 (±3)**
Informed Consent	x							
Demographics/Medical Hx	x							
Physical Examination	x						x	
Inclusion/Exclusion Criteria	x	x						
Body Weight	x	x					x	
Urinalysis/Pregnancy test	x	x					x	
Laboratory Tests	x						x	
Electrocardiogram (ECG)	x						x	
Vision testing	x						x	
Urodynamics (CMG)	x						x	
Renal Ultrasound	x				x		x	
Child Behaviour Questionnaire	x				x		x	
Vital Signs	x	x[3]	x	x	x	x	x	
Orthostatic test	x	x[3]	x	x	x	x	x	
Randomisation		x						
Snack/Meal		x	x	x	x			
Dispense Drugs		x	x	x	x	x		
Drug Administration in clinic		x	x	x	x			
PK Sampling					x[4]	x[4]		
Dispense Catheterisation Diary	x	x	x	x	x	x		
Collect Catheterisation Diary		x	x	x	x	x	x	
Adverse Events	x	x	x	x	x	x	x	x
Concomitant Therapy	x	x	x	x	x	x	x	x
Compliance Check			x	x	x	x	x	
Term. of Trial Medication							x	
Telephone Call								x
Trial Completion							x[5]	x[6]

1. Visit were performed for all patients inclusive of patients who terminate the trial early
2. Visit only for those who did not go into open label extension Trial 527.66
3. Vital signs at this visit were performed at -15 minutes, 1, 2 and 4 hours post-dose
4. PK sampling for Day 42 was at pre dose and at least 2 hours after the first sample. PK for Day 70 was 1st sample at least 6 hours post dose and 2nd sample at least 2 hours after 1st sample
5. Only for patients that continued on to Trial 527.66
6. Only for patients that did not continue into Trial 527.66

Inclusion criteria included:

1. Signed and dated written informed consent by the parent or guardian and, where appropriate, informed assent by the child, prior to admission into the study in accordance with GCP and the local legislation, has been obtained
2. Patients of either sex; ages 2–16 years inclusive, with a body weight of 12.5 kg to a maximum of 100 kg
3. Patients with a neuropathic bladder secondary to a known neurologic deficit (e.g., spina bifida). This includes children who are performing clean intermittent catheterization (CIC).
4. Patients with an elevated detrusor leak point pressures (LPP ≥40 cm H_2O) associated with a known neurological deficit and confirmed by two measurements on the same day, within 3 months prior to Visit 1

Exclusion criteria included:

1. Patients with clinically significant abnormalities (unrelated to the trial indication), found at, or before randomization (i.e., abnormal vital signs [e.g., hypotension], abnormal ECG), as well as clinically significant findings during the physical examination, as determined by the investigator
2. Patients with clinically significant conditions which, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence either the results of the study or the patient's ability to participate in the study. These conditions include, but are not limited to, the following: gastrointestinal, cardiovascular, hepatic, renal, hematologic, metabolic (including uncontrolled diabetes mellitus), immunological, hormonal disorders, respiratory disease, or cancer.
3. Patients with a history of relevant orthostatic hypotension, fainting spells or blackouts. Postural symptoms occurring (e.g., light-headedness, dizziness, and fainting) with or without a change in blood pressure and / or pulse rate within 6 weeks of Visit 1.
4. Patients with clinically significant laboratory abnormalities (based on investigator judgment) or laboratory values >2x times the upper limit of normal range
5. Patients with severe hydronephrosis > Grade 3. A renal ultrasound performed within 3 months prior to entering the study will be accepted as a baseline measurement if this assessment was performed while the patient was on a stable medication regimen.
6. Patients with a lifetime history of bladder neck surgery, bladder augmentation or permanently exteriorized bladder drainage procedures and those patients who have had any surgical procedure under general anesthesia within 30 days prior to Visit 2
7. Patients with a significant psychiatric disorder (based on investigator discretion) that prevents their comprehension of consent and their ability to comply with the protocol
8. Patients on drug therapy, or non-drug therapy including electro-stimulation for their neuropathic bladder initiated during the four weeks prior to screening or anticipated to initiate during the study
9. Patients who have a history of allergy / hypersensitivity (including drug and sulfa allergy) which is deemed relevant to the trial as judged by the investigator

10. Patients who use alpha-blockers (e.g., prazosin, terazosin, alfuzosin, doxazosin, tamsulosin) within 30 days of screening visit
11. Patients taking warfarin, ranitidine or cimetidine
12. Patients having a symptomatic (febrile) urinary tract infection at screening. After the UTI has been treated and stabilized (no longer symptomatic) the patient may be entered into the study.
13. Patients participating in another trial with an investigational drug within 1 month prior to screening or during the trial
14. Patients with a positive pregnancy test or a patient that is lactating. All female patients of child bearing potential, who are sexually active in the opinion of the investigator, must be using two accepted means of birth control.
15. Patients or their parents or guardians who, in the investigator's opinion cannot understand the terms of the informed consent form and / or subject information
16. Patients who have been treated with Botulinum Toxin Type A (Botox) injections for urologic use within 6 months of randomization at Visit 2
17. Patients who are or have been committed to an institution by virtue of an order either by the judicial or the administrative authorities

6.1.4 Efficacy Findings

Primary Endpoint
Detrusor Leak Point Pressure (LPP) was measured by a standard urodynamic procedure using calibrated electronic equipment upon which the investigator and / or clinical staff had been adequately trained. Accuracy of detrusor LPP was confirmed by performing independent tests within the same visit that indicate two values either equal to or above 40 cm H_2O, or two values below 40 cm H_2O. A maximum of three evaluations per visit were allowed in order to establish the two LPP values either equal to or above, or below 40 cm H_2O. The proportions of responders in each tamsulosin HCl dose group and the placebo group were compared for the FAS-LPP dataset.

A total of 135 patients were in the full analysis set (FAS-LPP) and were included in the primary analysis and showed a 37.8% overall response rate. The response rates for the placebo, low, medium and high tamsulosin dose groups were 35.3%, 45.7%, 27.3% and 42.4%, respectively. The proportion of responders in each of the dose groups was not statistically significant from that of the placebo group.

Table 8. Response rates by treatment group at Week 14 (FAS-LPP, OT)

		Tamsulosin Dose			
	Placebo	Low	Medium	High	Total
Number of Patients	34	35	33	33	135
LPP Responder N (%)	12 (35.3)	16 (45.7)	9 (27.3)	14 (42.4)	51 (37.8)
Odds Ratio 95% CI	--	1.38 (0.50, 3.80)	0.59 (0.20, 1.76)	1.41 (0.50, 3.97)	--
p-value	--	0.5388[1]	0.3430[1]	0.5209[1]	0.9436[2]

1 Dose group vs. placebo
2 Cochran-Armitage trend test
Source: Table 15.2.1.2: 1

The same analysis was performed for the per-protocol set (PPS-LPP), which excluded patients with important protocol violations which might have impacted patients' response to treatment. There were 115 patients included in this analysis with an overall response rate of 40.0%. The pattern of the individual response rates for the four treatment groups was very similar as that for the FAS-LPP. No statistically significant difference was found between the proportions of responders in any of the tamsulosin dose groups *vs* the placebo dose group.

Table 9. Response rates by treatment group at Week 14 (PPS-LPP)

		Tamsulosin Dose			
	Placebo	Low	Medium	High	Total
Number of Patients	30	28	30	27	115
LPP Responder N (%)	11 (36.7)	14 (50.0)	9 (30.0)	12 (44.4)	46 (40.0)
Odds Ratio 95% CI	--	1.56 (0.51, 4.78)	0.63 (0.20, 1.99)	1.45 (0.47, 4.51)	--
p-value	--	0.4388[1]	0.4279[1]	0.5236[1]	0.9455[2]

1 Dose group vs. placebo
2 Cochran-Armitage trend test
Source: Table 15.2.1.5: 1

Post-hoc subgroup analyses were performed and descriptive statistics were provided for age, weight, and anticholinergic use, which were considered clinically relevant baseline characteristics which could impact the treatment effect. Age groups were defined as 2 to <5 years, 5 to <10 years and 10 to 16 years, for which the numbers of patients were 29, 58 and 48, respectively. The corresponding response rates for age groups across all treatment groups were 48.3%, 36.2%, and 33.3%, respectively. Weight groups were defined as 12.5 to <25.1 kg, 25.1 to <50.1 kg and 50.1 to 100 kg, for which the total numbers of patients were 89, 34 and 12,

respectively. The corresponding response rates for weight groups across all treatment groups were 38.2%, 35.3% and 41.7%, respectively. The age and weight group did not appear to be associated with a noticeable LPP response rate.

There were 50 patients receiving baseline anti-cholinergic therapy and 85 patients not on anti-cholinergic therapy, with corresponding LPP response rates of 44.4% and 34.1%, respectively. The baseline anti-cholinergic use did not appear to be associated with a noticeable LPP response rate at Week 14

Supportive Secondary Endpoints

At baseline, the mean LPP for the placebo, low, medium and high dose tamsulosin groups were 58.5, 62.6, 63.3 and 57.0 cm H_2O, respectively. Change in LPP from baseline to the end of treatment at Week 14 between each dose group and the placebo group was compared for the FAS-LPP. The least squares mean changes from baseline to Week 14 for the placebo, low, medium and high dose group were -11.4, -17.6, -4.6 and -14.3 cm H_2O, respectively. No statistically significant difference in change in LPP from baseline to Week 14 between any dose group and the placebo group was found.

Table 10. Baseline and change from baseline in detrusor LPP by treatment group (FAS-LPP)

	Placebo	Tamsulosin Dose			Total
		Low	Medium	High	
Baseline					
Number of patients	41	40	39	41	161
Mean	58.5	62.6	63.3	57.0	60.3
SD	22.1	20.8	27.0	22.4	23.1
Change from baseline at Week 14					
Number of patients	30	32	31	33	
LSMeans	-11.4	-17.6	-4.6	-14.3	
SE	4.6	4.5	4.4	4.3	
Differences to Placebo					
p-value*		0.3097	0.2676	0.6265	
95% CI		(-18.22, 5.83)	(-5.28, 18.85)	(-14.84, 8.98)	

*ANCOVA model with covariates of age group, anti-cholinergic use at baseline and geographic region
Source: Table 15.2.1.3: 1

Renal ultrasounds were also conducted as a secondary efficacy endpoint and these showed no meaningful change from baseline in any group and no differences between placebo and active treatment groups.

6.1.5 Clinical Microbiology

No clinical microbiology data was included in this submission.

Efficacy Conclusions

The primary efficacy variable was Detrusor Leak Point Pressure measured by a standard urodynamic procedure. There was no statistically significant difference in the proportions of responders who achieved LPP <40 cm H_2O between any tamsulosin HCl dose group and the placebo group at Week 14. In addition, there was no statistically significant difference between any tamsulosin HCl dose group and the placebo group for any secondary urodynamic endpoint, nor for change in renal ultrasounds.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review consisted primarily of findings from pivotal trial BI 527.51 but also included long term safety data from study BI 527.66.

7.1.1 Deaths

One death (Patient 6082) was reported in the pivotal Phase III study BI 527.51. The 7 year old male patient received the first dose of study medication (low dose group) on 16 October 2008 followed by an uneventful clinical evaluation on 24 October 2008 (Visit 3/Week 1) and on 30 October 2008 (Visit 4/Week 2). The patient regularly took the study medication after breakfast under parental guidance with the last dose reported on 31 October 2008. On (b) (6) at 7 am, the patient's father called the trial coordinator and complained that the patient was sick. He reported that the patient was unresponsive since morning. The father was asked to bring the patient to the site immediately. The patient arrived at the site at 8:45 a.m., where he was found to be expired. Blood pressure and pulse were not recordable, heart sounds were absent, there were no respiratory movements and the pupils were dilated and non-reacting. The patient's parents did not agree to any kind of test or post mortem examination. They removed the dead patient from clinic against medical advice by 9:15 a.m. Hence, autopsy could not be performed. The parents did not respond to phone calls from the clinic.

The patient had a past medical history of myelomeningocele at L3-L5, Arnold Chiari malformation, hydrocephalous, neurogenic bladder with urinary incontinence, and bilateral congenital talipes equino varus (club feet). The patient did not have surgical repair of the neural tube defect, nor did he have any intervention for accompanying malformations. The patient did have a left nephrectomy for a nonfunctioning hydronephrotic kidney and a shunt for the chronic

hydrocephalus. The primary investigator found the cause of death to be indeterminate and the BI clinical monitor judged that the death was unrelated to the study medication (tamsulosin HCl 0.05 mg).

Reviewer's Comment: The reviewer concludes that the case narrative of the one death report was inconclusive due to lack of information.

7.1.2 Other Serious Adverse Events

Of the 161 patients who received at least one dose of study medication in Study BI 527.51, two patients experienced serious AEs: one in the tamsulosin HCl low dose group (Patient 6082 listed as a death above), and one in the placebo group (Patient 6003).

The case narrative for Patient 6003 was reviewed and was consistent with a neural shunt malfunction requiring surgical revision and hospitalization for post-operative complications. The primary investigator and BI clinical monitor determined the events to be unrelated to study medication.

Of the two SAEs reported during the study, one (death) occurred in the 5- to <10-year-old group and the other SAE occurred in the 10- to 16-year-old group (hospitalization in the placebo group).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Not including the death of Patient 6082 and the SAE of Patient 6003 who was hospitalized for CSF shunt malfunction, two additional patients discontinued study treatment due to AEs (Patients 5323 and 5281 discussed below).

There were no patients who discontinued study drug due to AE(s) in the 2- to <5-year-old group. Discontinuation of study drug due to AE(s) occurred in the 5- to <10-year-old group at a higher rate for placebo (5.6%) compared to tamsulosin HCl total (1.9%). In the 10- to 16-year old group, there were no patients that discontinued placebo as compared to 2.2% for tamsulosin HCl total.

7.1.3.2 Adverse events associated with dropouts

Patient 5323 was a 9-year-old female with a medical history of spina bifida and no history of surgical intervention for neural tube repair, CS shunt diversion, or surgical decompression. Patient was randomized to placebo and began treatment on 30 Sep 2008. On 21 Oct 2008, the

patient complained of severe headache along with moderate abdominal pain, mild nausea and vomiting. Vomiting resolved after 1 day but the other events continued, prompting the patient to discontinue study medication on 01 Nov 2008. The patient received trimethoprim sulfamethoxazole and metronidazole between 18 Nov 2008 and 24 Nov 2008. The patient recovered from all events.

Patient 5281 was a 12-year-old female with a medical history of an acquired primary neural defect and no history of surgical interventions. The patient was on ongoing therapy with oxybutynin for neurogenic bladder. The patient was randomized to low dose tamsulosin HCl and began treatment on 26 Feb 2008. On 25 Mar 2008 the patient experienced mild cardiac palpitations which resolved without treatment on 18 Apr 2008. On 28 May 2008 the patient experienced moderate pallor, palpitations, and sweating and discontinued from study treatment. No treatment was given and the patient recovered from all events.

7.1.3.3 Other significant adverse events

None

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The occurrence of adverse events was sought by non-directive questioning of the patient at each visit during the study. Adverse events were also detected when they were volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were evaluated to determine:

- the severity grade (mild, moderate, severe)
- its relationship to the study drug(s) (suspected/not suspected)
- its duration (start and end dates or if continuing at final exam)
- action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

A serious adverse event (SAE) was defined as one which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization

7.1.5.3 Incidence of common adverse events

Of the 161 patients who received at least one dose of study treatment, the overall percentage of AEs in each of the tamsulosin HCl treatment groups was 32.5% for low dose, 30.0% for medium dose, 37.5% for high dose, and 43.9% for placebo.

When comparing the incidence of AEs across the low, medium, and high doses of tamsulosin HCl, rates are calculated using the number of patients exposed to each dose at the onset of the AE. Therefore, because of the titration process, the total number of patients who at any time received a particular dose (the denominator) included 120, 80, and 40 patients at the low, medium, and high doses, respectively.

Table 11. Overall summary of adverse events, by treatment at onset (TS)

	Tamsulosin Dose				
Category, N (%)[a]	**Placebo**	**Low**	**Medium**	**High**	**Tams. HCl Total[b]**
Number of patients	41	120	80	40	120
Patients with any AE	18 (43.9)	39 (32.5)	24 (30.0)	15 (37.5)	67 (55.8)
Patients with severe AEs	2 (4.9)	1 (0.8)	1 (1.3)	0 (0.0)	2 (1.7)
Patients with investigator defined drug-related AEs	2 (4.9)	4 (3.3)	1 (1.3)	2 (5.0)	7 (5.8)
Patients with other significant AEs[c]	1 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Patients with AEs leading to discontinuation of trial drug	1 (2.4)	2 (1.7)	0 (0.0)	0 (0.0)	2 (1.7)
Patients with SAEs:	1 (2.4)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Fatal	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Required hospitalisation	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Percentages are calculated using total number of patients per treatment as the denominator

[b] The Total column includes patients receiving active doses only; patients are counted only once

[c] Defined as significant according to ICH E3 Guidelines: adverse events marked as haematological or other laboratory abnormalities (but not serious) or leading to intervention

Source: Table 15.3.2: 1

Overall, the rates of AEs presented by randomized dose were similar across the three tamsulosin HCl treatment groups. The most frequently reported AEs for placebo *vs* tamsulosin HCl total groups, respectively, were urinary tract infection (9.8% *vs* 11.7%), vomiting (12.2% *vs* 7.5%), nasopharyngitis (2.4% *vs* 9.2%), headache (14.6% *vs* 4.2%), influenza (7.3% *vs* 5.0%), and abdominal pain (14.6% *vs* 1.7%).

When grouped by system organ class (SOC), the highest incidence of AEs that occurred in the placebo *vs* tamsulosin HCl total groups, respectively, was observed in Infections and infestations (24.4% *vs* 30.8%), followed by Gastrointestinal disorders (29.3% *vs* 15.0%) and Nervous system disorders (17.1% *vs* 5.0%). The reported frequency of abdominal pain was higher among placebo patients (14.6% *vs* 1.7% for tamsulosin HCl total) as was constipation (7.3% *vs*. no incidences in the tamsulosin HCl groups). Respiratory tract infection was reported in 4.9% of placebo patients and 0% in the tamsulosin HCl groups and cough was reported in 0% of the placebo group and 5.0% in tamsulosin HCl patients.

7.1.5.4 Common adverse event tables

Table 12. Adverse events that occurred in at least 4% of patients in any treatment group

System organ class/ Preferred term, N (%)[a]	Placebo	Tamsulosin HCl Groups			Tams. HCl Total[b]
		Low	Medium	High	
Number of patients	41	40	39	41	120
Total with adverse events	18 (43.9)	22 (55.0)	22 (56.4)	23 (56.1)	67 (55.8)
Infections and infestations	**10 (24.4)**	**12 (30.0)**	**12 (30.8)**	**13 (31.7)**	**37 (30.8)**
Urinary tract infection	4 (9.8)	5 (12.5)	3 (7.7)	6 (14.6)	14 (11.7)
Nasopharyngitis	1 (2.4)	3 (7.5)	4 (10.3)	4 (9.8)	11 (9.2)
Influenza	3 (7.3)	2 (5.0)	2 (5.1)	2 (4.9)	6 (5.0)
Respiratory tract infection	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**12 (29.3)**	**2 (5.0)**	**7 (17.9)**	**9 (22.0)**	**18 (15.0)**
Abdominal pain	6 (14.6)	0	1 (2.6)	1 (2.4)	2 (1.7)
Vomiting	5 (12.2)	1 (2.5)	4 (10.3)	4 (9.8)	9 (7.5)
Constipation	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (2.4)	0 (0.0)	2 (5.1)	0 (0.0)	2 (1.7)
Diarrhea	2 (4.9)	2 (5.0)	0 (0.0)	2 (4.9)	4 (3.3)
Nausea	2 (4.9)	0 (0.0)	0 (0.0)	2 (4.9)	2 (1.7)
Nervous system disorders	**7 (17.1)**	**1 (2.5)**	**3 (7.7)**	**2 (4.9)**	**6 (5.0)**
Headache	6 (14.6)	1 (2.5)	3 (7.7)	1 (2.4)	5 (4.2)
Respiratory, thoracic and mediastinal disorders	**1 (2.4)**	**1 (2.5)**	**5 (12.8)**	**2 (4.9)**	**8 (6.7)**
Cough	0 (0.0)	0 (0.0)	5 (12.8)	1 (2.4)	6 (5.0)
General disorders and administration site conditions	**2 (4.9)**	**4 (10.0)**	**2 (5.1)**	**1 (2.4)**	**7 (5.8)**
Pyrexia	2 (4.9)	1 (2.5)	2 (5.1)	1 (2.4)	4 (3.3)

[a] Percentages are calculated using total number of patients randomised to each treatment as the denominator
[b] The Total column includes patients receiving active doses only; patients are counted only once
Source: Table 15.3.2: 9

7.1.5.5 Identifying common and drug-related adverse events

All AEs were coded using MedDRA terms and are summarized by primary system organ class (PSOC) and preferred term.

7.1.5.6 Additional analyses and explorations

The percentage of mild AEs reported for the placebo and tamsulosin HCl dosing groups were 19.5% (placebo), 28.3% (low), 22.5% (medium), and 45% (high).

The percentage of moderate AEs were higher for placebo (19.5%) than tamsulosin HCl dosing groups (3.3% -low , 6.3% -medium, 5% -high). Moderate AE rates were similar within the tamsulosin HCl groups, suggesting that there was no dose-response effect.

Table 13. Moderate adverse events in any treatment group

System organ class/ Preferred term	Mod Placebo N (%)	Tams-low N (%)	Tams-med N (%)	Tams-high N (%)	Tams-total N (%)
Number of patients	41 (100.0)	120 (100.0)	80 (100.0)	40 (100.0)	120 (100.0)
Total with adverse events	8 (19.5)	4 (3.3)	5 (6.3)	2 (5.0)	11 (9.2)
Infections and infestations	3 (7.3)	2 (1.7)	4 (5.0)	2 (5.0)	8 (6.7)
Urinary tract infection	2 (4.9)	1 (0.8)	0 (0.0)	1 (2.5)	2 (1.7)
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (1.3)	1 (2.5)	2 (1.7)
Influenza	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.8)
Respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.8)	1 (1.3)	0 (0.0)	2 (1.7)
Fungal infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Furuncle	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Measles	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.8)
Respiratory tract infection viral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Varicella	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Ascariasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Balanitis candida	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Laryngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tinea pedis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophilia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System organ class/ Preferred term	Mod Placebo N (%)	Tams-low N (%)	Tams-med N (%)	Tams-high N (%)	Tams-total N (%)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal dreams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (2.4)	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epilepsy	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Irregular sleep phase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular hyperaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerumen impaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Sinus tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Vascular disorders	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pallor	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)

System organ class/ Preferred term	Placebo N (%)	Tams-low N (%)	Mod Tams-med N (%)	Tams-high N (%)	Tams-total N (%)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (9.8)	0 (0.0)	1 (1.3)	2 (5.0)	3 (2.5)
Abdominal pain	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (4.9)	0 (0.0)	1 (1.3)	1 (2.5)	2 (1.7)
Constipation	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Loose tooth	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Lip dry	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis contact	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperhidrosis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Prurigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash papular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System organ class/ Preferred term	Placebo N (%)	Tams-low N (%)	Mod Tams-med N (%)	Tams-high N (%)	Tams-total N (%)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.8)
Enuresis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydronephrosis	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.8)
Incontinence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydroureter	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.8)
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Balanoposthitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epididymitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	1 (2.4)	1 (0.8)	0 (0.0)	1 (2.5)	2 (1.7)
Pyrexia	1 (2.4)	1 (0.8)	0 (0.0)	1 (2.5)	2 (1.7)
Thirst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Shunt malfunction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Forearm fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Excoriation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal fusion surgery	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The rate of severe AEs in patients receiving placebo was 4.9% (2 patients) and for those receiving active treatment it was 1.7% (2 patients). Among those receiving placebo, 1 patient experienced a severe headache (and moderate abdominal pain) for which he was discontinued from the study; another patient reported a severe headache and stiff neck, followed by a severe

CSF shunt malfunction for which he was hospitalized. Severe headache was the only severe AE reported by more than 1 patient; both AEs occurred in patients receiving placebo.

Of the two severe AEs in the tamsulosin HCl group, one AE occurred in a patient receiving low dose treatment and one AE in a patient receiving medium dose treatment. The patient receiving low dose tamsulosin HCl died of unknown causes. The intensity of the unknown event was recorded as severe due to the outcome. The other severe AE patient received medium dose treatment and experienced severe muscle spasms in the genital area.

7.1.6 Less Common Adverse Events

N/A

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The following laboratory tests were summarized, where * denotes a categorical variable:
• **Hematology**: Hemoglobin (g/L), Hematocrit (1), Platelet count (10E9/L), WBC (10E9/L), RBC (10E12/L), differential white blood cell counts [Basophils (%), Eosinophils (%), Monocytes (%), Lymphocytes (%), Neutrophils (%)]
• **Biochemistry**: Glucose (mmol/L), Creatinine (umol/L), Calculated creatinine clearance (mL/min), Blood urea nitrogen [BUN] (mmol/L), Uric acid (umol/L), Total protein (g/L), SGOT/AST (U/L), SGPT/ALT (U/L), Sodium (mmol/L), Potassium (mmol/L), Chloride (mmol/L), Phosphorus (mmol/L), Magnesium (mmol/L), Albumin (g/L), Calcium (mmol/L)
• **Urinalysis**: Specific gravity, Color (urine)*, Nitrite (urine)*, pH (urine), Protein (urine)*, Leukocytes (urine)*, Glucose (urine)*, Bilirubin (urine)*, Ketones (urine)*, Blood (urine)*, Microscopic (urine)*, Urobilinogen (U/dL)
• **Hormonal assays:** Prolactin, follicle stimulating hormone (FSH), estradiol, thyroxine 4 (T4), testosterone (free and total), thyroxine 3 (T3), and leutinizing hormone (LH).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The number and percentage of patients who had treatment-emergent clinically notable results in laboratory values are presented.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

There were no clinically relevant differences between the treatment groups for liver function test parameters of ALT, AST, and GGT.

Table 14. Liver Function Parameters

Parameter/	Baseline					Last Value on Treatment					Difference from Baseline				
Treatment	N	Min	Mean	SD	Max	N	Min	Mean	SD	Max	N	Min	Mean	SD	Max
AST/GOT, SGOT [U/L]															
Placebo	39	-2	21	10	42	32	-4	21	11	39	30	-14	-0	6	17
Tams-low	39	0	25	16	85	30	9	22	9	44	30	-49	-1	12	15
Tams-med	39	4	25	12	70	33	5	24	11	55	33	-24	0	10	31
Tams-high	41	4	24	9	49	37	5	22	9	51	37	-19	-2	8	21
ALT/GPT, SGPT [U/L]															
Placebo	40	-4	16	10	42	32	0	19	13	62	31	-14	3	10	36
Tams-low	39	2	21	17	74	31	5	21	14	82	31	-55	-1	18	44
Tams-med	39	-4	22	16	78	33	-4	21	13	56	33	-20	2	10	36
Tams-high	41	5	18	10	44	37	3	18	9	47	37	-30	-0	11	24
GGT [U/L]															
Placebo	41	14	32	14	80	34	12	31	12	59	34	-45	-2	10	13
Tams-low	39	11	46	95	621	33	12	28	9	55	33	-47	-4	10	7
Tams-med	39	11	31	11	55	34	11	30	11	59	34	-31	-1	8	17
Tams-high	41	12	31	14	85	38	12	28	10	52	38	-49	-3	13	16
LDH [U/L]															
Placebo	37	138	190	26	263	32	131	177	27	237	29	-49	-11	19	16
Tams-low	39	127	189	33	282	29	127	179	26	234	29	-81	-5	25	39
Tams-med	36	139	188	28	242	33	131	179	27	260	30	-44	-5	21	49
Tams-high	38	129	184	29	252	38	138	187	36	354	35	-55	2	34	140
Creatine kinase [U/L]															
Placebo	41	76	195	100	548	33	59	192	87	390	33	-287	-6	87	180
Tams-low	39	76	222	104	457	32	77	275	174	788	32	-194	56	120	387
Tams-med	39	86	232	135	737	33	86	212	112	556	33	-265	-2	91	234
Tams-high	41	65	218	114	501	37	77	221	92	426	37	-164	3	100	237

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

A summary of the laboratory parameters with at least three patients with notable post-baseline hematology and biochemistry abnormalities is presented. There were similar low frequency laboratory aberrations among the treatment groups.

Table 15. Hematology laboratory measures with 3 or more patients (per dose group) with shifts at end of treatment

Laboratory Measure/ Direction of Shift, N (%)[a]	Placebo N = 41	Tamsulosin HCl Groups		
		Low N = 40	Medium N = 39	High N = 41
Haematocrit				
Low to Normal	N/A	N/A	N/A	5 (12.2)
Normal to Low	N/A	N/A	N/A	4 (9.8)
Haemoglobin				
Low to Normal	N/A	N/A	N/A	4 (9.8)
Normal to Low	N/A	4 (10.5)	N/A	6 (14.6)
MCV				
Low to Normal	3 (8.1)	N/A	3 (7.7)	3 (7.3)
Normal to Low	N/A	N/A	N/A	4 (9.8)
MCHC				
Normal to Low	N/A	6 (15.8)	N/A	N/A
WBC				
High to Normal	4 (9.8)	N/A	N/A	5 (12.2)
Platelets				
Normal to High	4 (9.8)	5 (13.2)	N/A	3 (7.7)
High to Normal	N/A	3 (7.9)	3 (7.7)	4 (10.0)
RBC morphology				
Normal to High	N/A	3 (7.9)	N/A	3 (7.3)
High to Normal	N/A	N/A	4 (10.3)	N/A

[a] Percentages are based on the total of patients within each treatment group who had at least 1 baseline or last value (may differ from overall number of patients)
N/A - Not applicable since <3 patients represent this category
Source: Table 15.3.3: 4

Table 16. Chemistry laboratory measures with 3 or more patients (per dose group) with shifts at end of treatment

Laboratory Measure/ Direction of Shift, N (%)[a]	Placebo N = 41	Tamsulosin HCl Groups		
		Low N = 40	Medium N = 39	High N = 41
ALT				
High to Normal	N/A	3 (7.7)	N/A	N/A
Calcium				
Normal to High	N/A	N/A	4 (10.3)	N/A
High to Normal	4 (9.8)	5 (12.8)	N/A	7 (17.1)
Magnesium				
Normal to High	3 (7.3)	7 (17.9)	N/A	5 (12.2)
High to Normal	10 (24.4)	3 (7.7)	5 (12.8)	5 (12.2)
Creatine kinase				
Normal to High	N/A	4 (10.3)	N/A	N/A
High to Normal	3 (7.3)	N/A	N/A	3 (7.3)
Glucose				
Normal to High	4 (9.8)	N/A	N/A	3 (7.3)
High to Normal	N/A	N/A	N/A	4 (9.8)
Creatinine				
High to Normal	4 (9.8)	N/A	N/A	N/A
Uric acid				
Normal to High	3 (7.3)	N/A	N/A	N/A
Protein				
High to Normal	N/A	N/A	N/A	3 (7.3)
Bilirubin, total				
Low to Normal	4 (9.8)	N/A	3 (7.7)	N/A
Normal to Low	3 (7.3)	N/A	5 (12.8)	5 (12.2)
Cholesterol				
High to Normal	N/A	3 (7.3)	3 (7.3)	N/A
Low to Normal	3 (7.3)	N/A	N/A	N/A
Triglycerides				
Normal to High	7 (17.1)	10 (25.6)	12 (30.8)	10 (24.4)
High to Normal	5 (12.2)	12 (30.8)	N/A	9 (22.0)

[a] Percentages are based on grand total of patients within each treatment group who had at least 1 baseline or last value (may differ from overall number of patients)
N/A – Not applicable since <3 patients represent this category
Source: Table 15.3.3: 4

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

No laboratory abnormality caused a subject to discontinue from study participation.

7.1.7.4 Additional analyses and explorations

Two patients had treatment-emergent laboratory abnormalities that were reported as AEs. Patient 5568, a 4-year-old female randomized to low dose tamsulosin HCl, was reported to be anemic when treatment began at Visit 2 (04 Aug 2008). The anemia was considered mild and unrelated to study treatment and therapy was administered. She completed the study on 13 Nov 2008 and the anemia was noted to have resolved on 11 Jan 2009.

Patient 5701, a 4-year-old female randomized to high dose tamsulosin HCl, was reported to have eosinophilia on Day 86 (03 Oct 2008). The patient began study treatment on 26 Jun 2008 and completed treatment on 06 Oct 2008 according to protocol. Eosinophilia was noted to have resolved on 03 Nov 2008.

7.1.7.5 Special assessments

Hormonal Assays:

In total, there were 150 patients who had hormonal assays at Week 14. The hormones analyzed were:

Prolactin
Estradiol
Testosterone (free and total)
Thyroxine 3 (T3)
Thyroxine 4 (T4)
Leutinizing Hormone (LH)
Follicle Stimulating Hormone (FSH)

A summary of the hormonal laboratory parameters with at least three patients with notable post-baseline abnormalities or shifts are presented. There were similar low frequency laboratory aberrations for estradiol, free and total testosterone, and FSH among the treatment groups, none were considered clinically significant. There were no significant shifts from normal for the laboratory parameters of LH, T3, and T4.

Table 17. Hormonal assay measures with 3 or more patients (per dose group) with shifts at end of treatment

Laboratory Measure/ Direction of Shift, N (%)[a]	Placebo N = 41	Tamsulosin HCl Groups		
		Low N = 40	Medium N = 39	High N = 41
Estradiol				
Low to Normal	4 (9.8)	N/A	5 (12.8)	10 (24.4)
Normal to Low	N/A	4 (10.3)	5 (12.8)	5 (12.2)
Free testosterone				
Low to Normal	N/A	N/A	3 (12.5)	4 (16.0)
Normal to Low	N/A	N/A	4 (16.7)	N/A
Total testosterone				
Low to Normal	N/A	7 (17.9)	4 (10.3)	4 (9.8)
Normal to Low	N/A	3 (7.7)	5 (12.8)	N/A
FSH				
Normal to High	5 (12.2)	3 (7.7)	N/A	4 (9.8)
High to Normal	5 (12.2)	N/A	4 (10.3)	4 (9.8)
Leutinizing hormone				
High to Normal	3 (7.3)	N/A	N/A	N/A
Thyroxine 3				
Low to Normal	3 (7.3)	N/A	N/A	N/A
Thyroxine 4				
Low to Normal	3 (7.3)	N/A	N/A	3 (7.3)
Prolactin				
Normal to High	4 (9.8)	6 (15.4)	5 (13.2)	7 (17.1)
High to Normal	6 (14.6)	N/A	6 (15.8)	5 (12.2)

[a] Percentages are based on grand total of patients within each treatment group who had at least 1 baseline or last value (may differ from overall number of patients)
N/A – Not applicable since <3 patients represent this category
Source: Table 15.3.3: 4

For prolactin, there was a slightly higher frequency of shifts to values above the normal range for the tamsulosin HCl-treated patients compared to those receiving placebo in the overall number of patients. Specifically looking at patients who were at risk (low or normal at baseline), the shift to high laboratory values were 19%-placebo, 24%-low dose, 23.8%-medium dose, and 29.2%-high dose.

Table 18. Prolactin assay measures with shifts from low or normal to high laboratory values at end of treatment

Parameter/ Treatment	Last Value on Treatment: High, Norm to Low	at risk*	Low,Norm to High	at risk**	Min Post Baseline: High, Norm to Low	at risk*	Max Post Baseline: Low, Norm to High	at risk**
T3 (Triiodothyronine)								
Placebo	0	25	0	29	0	25	0	29
Tams-low	0	29	0	31	0	29	0	31
Tams-med	0	31	0	31	0	31	0	31
Tams-high	0	36	0	37	0	36	0	37
Prolactin								
Placebo	0	34	4 (19.0)	21	0	34	4 (19.0)	21
Tams-low	0	33	6 (24.0)	25	0	33	6 (24.0)	25
Tams-med	0	33	5 (23.8)	21	0	33	5 (23.8)	21
Tams-high	0	36	7 (29.2)	24	0	36	7 (29.2)	24

The normalized mean change in prolactin level from baseline to end of treatment ranged from -1.5 ng/ml for placebo to + 3.6 ng/ml for the high dose tamsulosin HCl dose group.

Table 19. Mean change in prolactin level

Parameter/ Treatment	Baseline: N	Min	Mean	SD	Max	Last Value on Treatment: N	Min	Mean	SD	Max	Difference from Baseline: N	Min	Mean	SD	Max
T3 (Triiodothyronine) [nmol/L]															
Placebo	41	0.07	1.50	0.56	2.68	29	0.39	1.47	0.41	2.24	29	-0.84	0.04	0.43	0.94
Tams-low	39	0.24	1.45	0.44	2.40	31	0.83	1.64	0.45	2.55	31	-0.59	0.21	0.41	1.03
Tams-med	39	0.49	1.58	0.43	3.03	32	0.91	1.66	0.41	2.68	32	-0.67	0.07	0.37	0.72
Tams-high	41	0.64	1.50	0.35	2.12	37	0.99	1.56	0.35	2.29	37	-0.62	0.07	0.39	0.89
Prolactin [ng/mL]															
Placebo	41	5.1	21.1	12.9	69.0	34	5.5	21.1	11.0	48.3	34	-51.2	-1.5	12.3	16.9
Tams-low	39	4.2	19.6	11.5	58.2	33	4.5	22.7	13.9	59.4	33	-23.8	3.3	11.6	23.7
Tams-med	38	3.9	19.7	10.8	53.8	33	8.3	21.3	11.7	50.3	33	-20.4	1.3	8.7	23.9
Tams-high	40	2.6	25.2	23.6	132.3	37	4.6	30.3	25.9	120.6	36	-45.7	3.6	25.0	101.6

Table 15.3.3.1, source appendix 16 2.8 3 (normalized values), module 5.22

The limited number of subjects (5-10%) with a mild increase of 7-17% in absolute prolactin levels is likely drug related. However, the short term clinical sequalae is not apparent in the current study population of pediatric patients with significant neurologic disorders. The sponsor also has not determined any clinical AEs due to the increases in prolactin levels.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Sitting and supine blood pressure, pulse rate, and weight were assessed at screening and at every study visit.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs at baseline were balanced across all four treatment groups. Sitting and supine mean systolic and mean diastolic blood pressure in patients randomized to placebo and tamsulosin HCl groups were analyzed.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

There was a slight trend toward decreased supine mean systolic and mean diastolic blood pressure in patients randomized to the high dose tamsulosin HCl group. These changes from baseline appear to increase with the titration to higher levels of tamsulosin HCl. However, the mean decrease in SBP and DBP at the highest tamsulosin dose is limited to less than 2mm Hg.

Table 20. Mean change from baseline in supine blood pressure at Week 14 by treatment group

Vital Parameter	Placebo	Tamsulosin HCl Groups			Total
		Low	Medium	High	
Baseline[a] Mean (SD)					
N	41	40	39	41	161
SBP, mm Hg	108.1 (15.4)	106.8 (11.4)	105.8 (11.8)	106.7 (11.2)	106.9 (12.5)
DBP, mm Hg	69.3 (12.5)	68.8 (9.5)	67.3 (9.4)	67.2 (7.5)	68.1 (9.9)
Mean (SD) Change from Baseline Week 14					
N	37	37	38	40	152
SBP, mm Hg	0.7 (13.5)	0.8 (9.1)	1.2 (9.4)	-1.8 (11.0)	0.2 (10.8)
DBP, mm Hg	-0.2 (11.3)	-0.4 (8.2)	-0.0 (5.9)	-0.9 (7.6)	-0.4 (8.4)

[a] Baseline measurement for a patient was obtained using the mean of 3 observations for systolic and diastolic readings
Source: Table 15.3.4.1: 1

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

There was no incidence of a clinically notable vital sign change.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

No study discontinuation was reported due to vital sign changes.

7.1.8.4 Additional analyses and explorations

Orthostatic testing was conducted in conjunction with vital signs. The orthostatic measurement was the difference between seated and supine measurements after the patient sat upright for 2 minutes following a 5 to 10 minute rest in the supine position. Orthostatic hypotension was defined as a 20 mmHg drop in systolic blood pressure during orthostatic testing.

Overall, there was a low occurrence of orthostatic hypotension and the few incidences recorded were balanced between the placebo and active treatment groups. Three patients each had a single occurrence of orthostatic hypotension, including one patient who was receiving placebo (Patient 5569 at Week 2) and two who were receiving low dose tamsulosin HCl (Patient 5282 at Visit 2 at 4 hours post dose and Patient 5281 at Visit 5). None of these events was reported as an AE, Patient 5281 discontinued study medication prematurely due to other cardiovascular adverse events.

Table 21. Patients with clinically significant orthostatic tests* by treatment group and visit

		Placebo	Tams-low	Tams-medium	Tams-high	Total
		N/Total N(%)	N/Total N(%)	N/Total N(%)	N/Total N(%)	N/Total N(%)
Number of Patients		41	40	39	41	161
Baseline		40	38	36	40	154
Visit 2	-15 min	0/40 (0.0)	0/40 (0.0)	0/38 (0.0)	0/41 (0.0)	0/159 (0.0)
	1 hour	0/41 (0.0)	0/40 (0.0)	0/39 (0.0)	0/41 (0.0)	0/161 (0.0)
	2 hours	0/41 (0.0)	0/39 (0.0)	0/39 (0.0)	0/41 (0.0)	0/160 (0.0)
	4 hours	0/39 (0.0)	1/38 (2.6)	0/39 (0.0)	0/41 (0.0)	1/157 (0.6)
Visit 3		0/41 (0.0)	0/40 (0.0)	0/39 (0.0)	0/41 (0.0)	0/161 (0.0)
Visit 4		1/40 (2.5)	0/40 (0.0)	0/39 (0.0)	0/40 (0.0)	1/159 (0.6)
Visit 5		0/40 (0.0)	1/38 (2.6)	0/38 (0.0)	0/39 (0.0)	1/155 (0.6)
Visit 6		0/39 (0.0)	0/36 (0.0)	0/36 (0.0)	0/40 (0.0)	0/151 (0.0)
Visit 7		0/37 (0.0)	0/37 (0.0)	0/38 (0.0)	0/40 (0.0)	0/152 (0.0)

7.1.9 Electrocardiograms (ECGs)

The overall incidence of changes in ECGs from baseline to end of study was balanced across all treatment groups. 73.2% of patients in the placebo group had a normal ECG interpretation at end of study vs 79.5% of tamsulosin HCl treated patients. By the end of study, the placebo group had higher rate of new clinically abnormal ECG findings compared to active treatment groups: 14.6% in the placebo group vs 5%, 2.6%, and 4.9% in the low, medium and high dose tamsulosin HCl groups, respectively. The abnormal ECG findings represented conduction and

rhythm abnormalities. No patients had new onset abnormal changes in ST-segment length or T- or U-wave.

Table 21. Frequency of patients by overall clinical ECG interpretation and findings impacting interval measurement:

	Placebo N(%)	Tams-low N(%)	Tams-medium N(%)	Tams-high N(%)	Total N(%)
Number of patients	41(100.0)	40(100.0)	39(100.0)	41(100.0)	161(100.0)
Clinical ECG interpretation Normal					
Yes	30(73.2)	32(80.0)	34(87.2)	32(78.0)	128(79.5)
No, but normal at baseline	6(14.6)	2(5.0)	1(2.6)	2(4.9)	11(6.8)
No, and not normal at baseline	2(4.9)	3(7.5)	1(2.6)	5(12.2)	11(6.8)
Unable to evaluate	0(0.0)	0(0.0)	1(2.6)	1(2.4)	2(1.2)
Missing**	2(4.9)	3(7.5)	1(2.6)	1(2.4)	7(4.3)
New onsets of any abnormal findings					
Baseline normal	22(53.7)	17(42.5)	22(56.4)	19(46.3)	80(49.7)
No abnormalities at visit 7	15(36.6)	14(35.0)	15(38.5)	10(24.4)	54(33.5)
Any abnormality at visit 7	6(14.6)	3(7.5)	6(15.4)	9(22.0)	24(14.9)
Missing visit 7 measurement	1(2.4)	0(0.0)	1(2.6)	0(0.0)	2(1.2)
Baseline other*	17(41.5)	23(57.5)	16(41.0)	21(51.2)	77(47.8)
Baseline unable to evaluate	1(2.4)	0(0.0)	1(2.6)	0(0.0)	2(1.2)

The rate of new onset of any abnormal findings was comparable across all treatment groups: 6 (14.6%) in the placebo group and 3 (7.5%), 6 (15.4%) and 9 (22%) in the low, medium and high dose tamsulosin HCl groups, respectively.

One clinically significant ECG-related finding occurred during the study and it was therefore reported as an AE. Patient 5701, a 4-year-old female randomized to high dose tamsulosin HCl, experienced the AE of mild sinus tachycardia at Week 14. The event was not treated and was not judged to be drug-related; the event resolved in a day.

7.1.10 Immunogenicity

No immunogenicity data was submitted in this NDA.

7.1.11 Human Carcinogenicity

No human carcinogenicity data was submitted in this NDA.

7.1.12 Special Safety Studies

Post void residual measurements were obtained at baseline and at end of treatment to assess for any adverse effects on bladder function. At baseline, median post void residual for all patients was 34.50 mL. High level of variability in post void residual measurements was noted within each treatment group. At end of treatment, no significant change in mean post void residual volume was noted.

Renal Ultrasound assessment in all treatment groups showed either stabilization or improvement in hydroureter (94-100%) and hydronephrosis (88-97%) at Week 14. The large majority were stabilized hydroureter in patients with little or no hydroureter at baseline. There were no statistically significant differences in the number of tamsulosin-treated patients who showed a response for hydroureter or hydronephrosis at Week 14 when compared with placebo-treated patients. The overall treatment duration was not likely sufficient to reach any meaningful conclusions regarding improvement or stabilization of hydroureter or hydronephrosis. In addition, patients with severe hydronephrosis were excluded from study participation.

Visual acuity testing was conducted by the study coordinator at baseline and Week 14 using age-appropriate testing methods. In terms of visual acuity, there did not appear to be differences between placebo and tamsulosin HCl treatment groups, nor did there appear to be a trend among the tamsulosin HCl treatment groups suggesting a dose-response effect. The rate of decrease in visual acuity of the right eye reported by placebo group was 14.6% *vs* 5%, 12.8%, and 9.8% in the low, medium, and high dose groups, respectively. The rate of decrease in visual acuity of the left eye reported by placebo group was 9.8% *vs* 10%, 12.8, and 14.6% in the low, medium, and high dose groups, respectively.

Attention problems as an aspect of cognition was measured by the Achenbach Child Behavior Checklist (CBCL). Overall, low level aberrations were noted and were not sufficient to reach any meaningful conclusions. For patients aged 2- to 5-years with assessments at Week 14, 43 patients had a normal baseline score, 2 patients had a baseline borderline score, and 2 patients had a baseline clinical score for Attention Problems. Two patients improved from a baseline borderline to a normal score and 11 patients shifted from a baseline clinical to a borderline score for attention problems at Week 14.

For patients aged 6- to 16-years with assessments at Week 14, 75 patients had a normal baseline score, 10 patients had a baseline borderline score, and 9 patients had a baseline clinical score for Attention Problems. Three patients declined from a normal baseline to a borderline score and 1 patient declined from a baseline borderline to a clinical score for Attention Problems. Alternately, 6 patients improved from a baseline borderline to a normal score, 2 patients improved from a baseline clinical to a normal score, and 3 patients shifted from a baseline clinical to a borderline score for Attention Problems at Week 14.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Therapy with tamsulosin HCl has not been previously associated with withdrawal or abuse potential, and no new data addressing these issues was submitted in this NDA.

7.1.14 Human Reproduction and Pregnancy Data

This is a Pregnancy B category drug. Pregnancy tests were performed for post-menarchal females of child-bearing potential at screening, prior to the first dose and at the end of study. No positive pregnancy results were reported during the study.

7.1.15 Assessment of Effect on Growth

There is no expected effect on growth in the study population.

7.1.16 Overdose Experience

Clinical experience with acute overdosage of tamsulosin HCl is limited. No new cases of overdosage were described in this NDA.

7.1.17 Postmarketing Experience

Postmarketing experience with tamsulosin HCl in the pediatric population is limited since tamsulosin HCl is not presently approved for use in children by the Agency.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study BI 527.51 was a phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tamsulosin HCl to placebo in the reduction of detrusor leak point pressure in children with neuropathic bladders. The study was conducted in centers in the Americas, Asia, and Europe. A total of 161 patients randomized into the study received at least one dose of study medication and are included in the intent-to-treat and safety populations.

Stratification was defined by the 2 to <5 years age group, 5 to <10 years age group, and 10 to 16 years age group. Patients were also stratified based upon concomitant use of anti-cholinergic medication into two strata, yes or no.

7.2.1.2 Demographics

Children 2-16 years of age with elevated detrusor leak point pressure due to neurologic disorders were randomized into the study treatment groups. Of the 161 patients in the treatment set (TS), 60.2% were male. The mean age was 8.2 years, with 18.6% in the 2 to <5 age group, 43.5% of patients in the 5 to <10 year age group and 37.9% of patients in the 10 to 16 year age group. A total of 55.3% of patients were Asian, 27.3% were White, 11.2% were American Indian / Alaskan Native, and 6.2% were Black / African American. A total of 15.5% of patients were of Hispanic or Latino heritage.

The baseline demographic characteristics of the patients in the study treatment groups were comparable for race, gender, weight, anti-cholinergic use, and age.

Table 22. Patient baseline demographics, N (%) of TS

	Tamsulosin Dose Group				
	Placebo	**Low**	**Medium**	**High**	**Total**
Number of patients	41	40	39	41	161
Gender, N (%)					
Male	25 (61.0)	22 (55.0)	25 (64.1)	25 (61.0)	97 (60.2)
Female	16 (39.0)	18 (45.0)	14 (35.9)	16 (39.0)	64 (39.8)
Age (years)					
Mean	8.4	8.1	8.1	8.2	8.2
SD	3.7	4.2	3.8	4.3	4.0
Min	2.0	2.0	3.0	2.0	2.0
Median	8.0	7.0	7.0	7.0	7.0
Max	15.0	16.0	15.0	16.0	16.0
Grouped age (years), N (%)					
2 to < 5 years	7 (17.1)	8 (20.0)	7 (17.9)	8 (19.5)	30 (18.6)
5 to < 10 years	18 (43.9)	17 (42.5)	17 (43.6)	18 (43.9)	70 (43.5)
10 to 16 years	16 (39.0)	15 (37.5)	15 (38.5)	15 (36.6)	61 (37.9)
Race, N (%)					
American Indian/Alaska Native	5 (12.2)	3 (7.5)	5 (12.8)	5 (12.2)	18 (11.2)
Asian	23 (56.1)	22 (55.0)	21 (53.8)	23 (56.1)	89 (55.3)
Black/African American	6 (14.6)	1 (2.5)	2 (5.1)	1 (2.4)	10 (6.2)
White	7 (17.1)	14 (35.0)	11 (28.2)	12 (29.3)	44 (27.3)
Hispanic/Latino, N (%)					
No	35 (85.4)	35 (87.5)	33 (84.6)	33 (80.5)	136 (84.5)
Yes	6 (14.6)	5 (12.5)	6 (15.4)	8 (19.5)	25 (15.5)
Weight group (kg), N (%)					
12.5 to < 25.1 kg	24 (58.5)	26 (65.0)	22 (56.4)	24 (58.5)	96 (59.6)
25.1 to < 50.1 kg	15 (36.6)	9 (22.5)	13 (33.3)	14 (34.1)	51 (31.7)
50.1 to 100 kg	2 (4.9)	5 (12.5)	4 (10.3)	3 (7.3)	14 (8.7)
Anti-cholinergic use, N (%)					
No	25 (61.0)	26 (65.0)	24 (61.5)	23 (56.1)	98 (60.9)
Yes	16 (39.0)	14 (35.0)	15 (38.5)	18 (43.9)	63 (39.1)

Percentages may not add up to 100% due to rounding.
Source: Table 15.1.4: 1

The majority of patients had a diagnosis of myelomeningocele (56.5%), other spina bifida (11.8%), and meningocele (5%) as the primary neurologic disorder. The baseline characteristics pertaining to the neurologic disorder of the patients were comparable among the treatment groups.

Table 23. CNS-specific baseline characteristics by treatment group, N (%) of TS

		Tamsulosin Dose Group			
	Placebo	Low	Medium	High	Total
Number of patients	41	40	39	41	161
Primary neural tube defect [N(%)]					
Myelomeningocele	25 (61.0)	21 (52.5)	21 (53.8)	24 (58.5)	91 (56.5)
Meningocele	2 (4.9)	3 (7.5)	2 (5.1)	2 (4.9)	9 (5.6)
Other spina bifida	5 (12.2)	3 (7.5)	5 (12.8)	6 (14.6)	19 (11.8)
Occult dysraphism	3 (7.3)	1 (2.5)	2 (5.1)	0	6 (3.7)
Other dysraphism	4 (9.8)	5 (12.5)	5 (12.8)	4 (9.8)	18 (11.2)
Acquired defects	2 (4.9)	7 (17.5)	4 (10.3)	5 (12.2)	18 (11.2)
Highest segmental level involved [N(%)]					
Cervical	0	0	0	2 (5.0)	2 (1.3)
Thoracic	7 (17.5)	3 (7.9)	2 (5.4)	4 (10.0)	16 (10.3)
Lumbar	24 (60.0)	22 (57.9)	20 (54.1)	22 (55.0)	88 (56.8)
Sacral	9 (22.5)	13 (34.2)	15 (40.5)	12 (30.0)	49 (31.6)
Other malformations [N(%)]					
Hydrocephalus	12 (29.3)	11 (27.5)	13 (33.3)	11 (26.8)	47 (29.2)
Type II chiari malformation	4 (9.8)	2 (5.0)	2 (5.1)	5 (12.2)	13 (8.1)
Cranial nerve impairment	1 (2.4)	0	0	0	1 (0.6)
Other cranial/spinal malformations	4 (9.8)	2 (5.0)	5 (12.8)	7 (17.1)	18 (11.2)
ENT malformations	1 (2.4)	0	0	0	1 (0.6)
Gastrointestinal malformations	1 (2.4)	2 (5.0)	1 (2.6)	0	4 (2.5)
Duplicated ureter	1 (2.4)	0	0	0	1 (0.6)
Other urinary tract malformations	1 (2.4)	3 (7.5)	5 (12.8)	1 (2.4)	10 (6.2)
Lower extremity contractions and/or malformations	9 (22.0)	11 (27.5)	7 (17.9)	12 (29.3)	39 (24.2)
Joint dislocations	2 (4.9)	1 (2.5)	3 (7.7)	3 (7.3)	9 (5.6)
Kyphosis / scoliosis	10 (24.4)	3 (7.5)	8 (20.5)	8 (19.5)	29 (18.0)
Surg repair of neural tube defect [N(%)]	32 (78.0)	25 (62.5)	23 (60.5)	32 (80.0)	112 (70.4)
CSF shunt diversion [N(%)]	11 (27.5)	9 (22.5)	11 (28.9)	11 (28.2)	42 (26.8)
Surgical decompression [N(%)]	2 (5.0)	1 (2.5)	1 (2.6)	2 (5.3)	6 (3.8)
Orthopaedic interventions[N(%)]	8 (22.2)	5 (13.2)	7 (18.4)	7 (19.4)	27 (18.2)
Other interventions [N(%)]	4 (11.8)	3 (8.1)	2 (6.1)	3 (8.8)	12 (8.7)

Percentages are calculated based upon the total numbers of patients without missing values.
Source: Table 15.1.4: 5

Approximately half of the patients (50.3%) had at least one concomitant diagnosis. Overall, infections and infestations were reported for 18.6% of patients, with 9.3% of patients reporting urinary tract infections. A total of 15.5% of patients experienced renal and urinary disorders prior to the study, of which 6.2% of patients experienced enuresis and 3.1% of

patients experienced hydronephrosis. The baseline concomitant diagnoses were generally well balanced across treatment groups.

Table 24. Concomitant diagnoses by treatment group

System organ class/ Preferred term	Placebo N(%)	Tams-low N(%)	Tams-medium N(%)	Tams-high N(%)	Total N (%)
Number of patients	41(100.0)	40(100.0)	39(100.0)	41(100.0)	161(100.0)
Number of patients with at least one other concomitant diagnosis	21(51.2)	20(50.0)	24(61.5)	16(39.0)	81(50.3)
Infections and infestations	7(17.1)	9(22.5)	6(15.4)	8(19.5)	30(18.6)
Abdominal abscess	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Abscess	0(0.0)	0(0.0)	0(0.0)	1(2.4)	1(0.6)
Bronchitis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	1(0.6)
Cystitis	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Gastroenteritis	0(0.0)	1(2.5)	0(0.0)	0(0.0)	1(0.6)
Influenza	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Nasopharyngitis	0(0.0)	1(2.5)	0(0.0)	0(0.0)	1(0.6)
Otitis media	0(0.0)	1(2.5)	0(0.0)	0(0.0)	1(0.6)
Pyelonephritis chronic	2(4.9)	2(5.0)	1(2.6)	0(0.0)	5(3.1)
Rhinitis	0(0.0)	1(2.5)	0(0.0)	0(0.0)	1(0.6)
Subcutaneous abscess	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Upper respiratory tract infection	0(0.0)	0(0.0)	0(0.0)	1(2.4)	1(0.6)
Urinary tract infection	3(7.3)	4(10.0)	3(7.7)	5(12.2)	15(9.3)
Renal and urinary disorders	6(14.6)	4(10.0)	8(20.5)	7(17.1)	25(15.5)
Cystitis glandularis	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Cystitis noninfective	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Enuresis	3(7.3)	2(5.0)	2(5.1)	3(7.3)	10(6.2)
Hydronephrosis	3(7.3)	0(0.0)	1(2.6)	1(2.4)	5(3.1)
Hydroureter	0(0.0)	0(0.0)	0(0.0)	1(2.4)	1(0.6)
Incontinence	1(2.4)	1(2.5)	2(5.1)	1(2.4)	5(3.1)
Renal failure chronic	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Ureteric dilatation	0(0.0)	1(2.5)	0(0.0)	0(0.0)	1(0.6)
Ureteric stenosis	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Urinary incontinence	0(0.0)	1(2.5)	1(2.6)	1(2.4)	3(1.9)
Vesical fistula	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Vesicoureteric reflux	1(2.4)	0(0.0)	0(0.0)	1(2.4)	2(1.2)
Nervous system disorders	6(14.6)	6(15.0)	7(17.9)	5(12.2)	24(14.9)
Autonomic nervous system imbalance	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)

System organ class/ Preferred term	Placebo N(%)	Tams-low N(%)	Tams-medium N(%)	Tams-high N(%)	Total N (%)
Cerebral atrophy	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Convulsion	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Epilepsy	0(0.0)	1(2.5)	1(2.6)	0(0.0)	2(1.2)
Hydrocephalus	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Hyporeflexia	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Mild mental retardation	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Monoplegia	0(0.0)	0(0.0)	0(0.0)	1(2.4)	1(0.6)
Muscle contractions involuntary	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Muscle spasticity	0(0.0)	0(0.0)	0(0.0)	1(2.4)	1(0.6)
Myoclonic epilepsy	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Paraparesis	0(0.0)	2(5.0)	2(5.1)	0(0.0)	4(2.5)
Paraplegia	2(4.9)	3(7.5)	0(0.0)	2(4.9)	7(4.3)
Spinal cord disorder	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Syringomyelia	0(0.0)	0(0.0)	1(2.6)	2(4.9)	3(1.9)
Tethered cord syndrome	2(4.9)	1(2.5)	1(2.6)	1(2.4)	5(3.1)
Gastrointestinal disorders	3(7.3)	8(20.0)	4(10.3)	5(12.2)	20(12.4)
Constipation	3(7.3)	7(17.5)	2(5.1)	4(9.8)	16(9.9)
Faecal incontinence	0(0.0)	1(2.5)	0(0.0)	0(0.0)	1(0.6)
Gastric ulcer	0(0.0)	0(0.0)	0(0.0)	2(4.9)	2(1.2)
Inguinal hernia	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Megacolon	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Congenital, familial and genetic disorders	7(17.1)	3(7.5)	4(10.3)	2(4.9)	16(9.9)
Anal atresia	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Arnold-Chiari malformation	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Caudal regression syndrome	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Congenital absence of vertebra	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Congenital central nervous system anomaly	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Cryptorchism	2(4.9)	1(2.5)	0(0.0)	0(0.0)	3(1.9)
Double ureter	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Hypospadias	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Kidney duplex	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Kidney malformation	0(0.0)	0(0.0)	1(2.6)	0(0.0)	1(0.6)
Limb malformation	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Moebius II syndrome	0(0.0)	1(2.5)	0(0.0)	0(0.0)	1(0.6)

7.2.1.3 Extent of exposure (dose/duration)

The clinical trial consisted of two study periods:

- Study Period I, double-blind, dose titration period of 2 weeks

- Study Period II, a double-blind maintenance treatment period of 3 months

For the duration of the study, each dose of study medication consisted of two capsules. The combined contents of these two capsules were then sprinkled on a single teaspoonful of applesauce or yogurt. Each patient was instructed to take a teaspoonful of water immediately after swallowing the applesauce or yogurt containing the study medication.

Based on the mg/kg exposure range in adults, a dosing scheme for children was developed. Three active dose groups were selected (low, medium and high dose level) based upon body weight. Due to the modified-release formulation characteristics of tamsulosin hydrochloride capsules, three weight groups were selected, 12.5 to 25 kg, 25.1 to 50 kg, and 50.1 to 100 kg for mg/kg dosing.

Table 25. Selected tamsulosin hydrochloride dosing schema

Weight (kg)	tamsulosin HCl Low dose (0.001 – 0.002 mg/kg)	tamsulosin HCl Medium dose (0.002 – 0.004 mg/kg)	tamsulosin HCl High dose (0.004 – 0.008 mg/kg)	Placebo
12.5 – 25.0	0.025 mg	0.05 mg	0.1 mg	x
25.1 – 50.0	0.05 mg	0.1 mg	0.2 mg	x
50.1 – 100.0	0.1 mg	0.2 mg	0.4 mg	x

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Study BI 527.66:
In addition to the safety data from the pivotal randomized Study BI 527.51, the sNDA also includes safety information from a long term open-label safety Study BI 527.66. The inclusion and exclusion criteria of this long term safety study were essentially identical to Study BI 527.51. The study consists of three separate populations of children with elevated detrusor leak point pressure; including an initial PK / PD study patients, Group D – Denovo, and Group D - 527.51 rollover patients. Due to early study termination and parallel conduction of Studies 527.51 and 527.66, the long term safety study report did not include Group D - 527.51 rollover patients, although safety data for these rollover patients (96 patients) was submitted as a safety update to the completed study and is summarized in Section 7.2.9 of this review. Hence, the 88 patients included in the study report represent 31 patients who participated in the initial PK section of the study as well as 57 patients enrolled directly into the safety study (Group D-denovo). One patient was entered into the study, but failed to take any study medication (Patient 1042), resulting in a treated patient population of 87 patients (30 PK, 57 Denovo) in Study 66.

Weight based dosing schema for study BI 527.66 was identical to that utilized in the pivotal phase III study BI 527.51. Patients in the denovo group started the study at the Low Dose level, with the exception of the children with a body weight between nine and 12 kg (they started at the Medium Dose level), and titrated up to higher dose levels on a weekly basis until an efficacious level was reached. The patients remained on their efficacious dose level for the remainder of the study. If an efficacious dose level was not reached by Day 60 the patient could continue in the study at the discretion of the investigator. Adequate numbers of patients were enrolled to ensure that approximately 50 patients completed 12 months of treatment and at least 75 patients would complete at least 6 months of treatment. The mean duration of tamsulosin HCl treatment was 327.4 days (46.7 weeks) for a planned 52 week study period. 73 (84%) patients completed 12 months of tamsulosin treatment and 77 (89%) completed at least 6 months of tamsulosin HCl treatment.

Table 26. Patient disposition

	Tamsulosin Dose Level			
	Low	**Medium**	**High**	**Total**
Enrolled	- -	- -	- -	130
Not Entered/Randomised	- -	- -	- -	42
Entered/Randomised	- -	- -	- -	88
Not treated	- -	- -	- -	1[a]
Treated, N (%)	29 (100.0)	21 (100.0)	37 (100.0)	87 (100.0)
Completed Treatment, N (%)	27 (93.1)	16 (76.2)	30 (81.1)	73 (83.9)
Prematurely Discontinued from Treatment, N (%):				
N	2 (6.9)	5 (23.8)	7 (18.9)	14 (16.1)
AE (unexpected worsening of disease under study)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE (unexpected worsening of pre-existing disease)	0 (0.0)	1 (4.8)	0 (0.0)	1 (1.1)
AE (other)	2 (6.9)	3 (14.3)	0 (0.0)	5 (5.7)
Non-compliance	0 (0.0)	0 (0.0)	1 (2.7)	1 (1.1)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent Withdrawn (not due to AE)	0 (0.0)	1 (4.8)	3 (8.1)	4 (4.6)
Other	0 (0.0)	0 (0.0)	3 (8.1)	3 (3.4)

Patients are classified according to the treatment they were taking at Week 52 or end of treatment.
[a] Patient 1042 was randomized but never took drug.
Source: Table 15.1.1: 3

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. They included the regular assessments

of vital signs, orthostatic testing, physical exam, ECGs, vision, cognitive testing, and monitoring of hematology, blood chemistry, and urine. Throughout the study, the dose of tamsulosin HCl could have been adjusted at the investigator's discretion for safety reasons, with the exception of the PK section of the study. There were no plans to perform any statistical hypothesis testing for this open-label trial.

Nine patients experienced one or more serious adverse events (SAEs) during the treatment phase of the study; 2, 3, and 4 patients in the low, medium, and high dose groups, respectively. 71 (81.6%), 4 (4.6%), and 4 (4.6%) patients had a primary diagnosis of myelomeningocele, meningocele, and spina bifida, respectively. Case narratives of all SAEs were reviewed and the SAEs are not considered related to study medication. The SAEs are primarily associated with sequalae and complications of the primary neurologic disorder under study. A dose proportional effect in the rate of serious, severe, or overall adverse events is not observed. No deaths occurred during the study.

Table 27. Overview of adverse events analyzed by dose at end of treatment

	Tamsulosin Dose Group			
Category, N (%) of Patients	**Low**	**Medium**	**High**	**Total**
Total number of patients receiving dose at end of treatment	29	21	37	87
Patients with any AE, n (%)	29 (100.0)	19 (90.5)	31 (83.8)	79 (90.8)
Patients with Related AEs	4 (13.8)	4 (19.0)	0 (0.0)	8 (9.2)
Patients with Severe AEs	4 (13.8)	4 (19.0)	2 (5.4)	10 (11.5)
Patients with other Significant AEs[a]	2 (6.9)	4 (19.0)	0 (0.0)	6 (6.9)
Patients with AEs leading to discontinuation of study drug	2 (6.9)	4 (19.0)	0 (0.0)	6 (6.9)
Patients with Serious AEs[b]	2 (6.9)	3 (14.3)	4 (10.8)	9 (10.3)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immediately Life Threatening	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.1)
Disability / Incapacitated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Required Hospitalization	2 (6.9)	3 (14.3)	4 (10.8)	9 (10.3)
Prolonged Hospitalization	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.1)
Congenital Anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.1)

Percentages are calculated based on the number of patients per treatment as the denominator.
a Defined as significant according to ICH E3 Guidelines: adverse events marked as hematological or other laboratory abnormalities (but not serious) or leading to intervention.
b Patients may be counted in more than one serious criterion or dose group (due to titration for efficacy).
Source: Table 15.3.2.1: 2

2 patients in the low dose and 4 patients in the medium dose treatment groups discontinued treatment due to adverse events.

A total of 79 (90.8%) patients experienced adverse events while receiving tamsulosin HCl during the study. 9.2% of adverse events were considered related to study medication and 11.5% were severe in intensity. The most frequently reported AEs were urinary tract infection (41.4% of patients), pyrexia (23.0%), vomiting (17.2%), pharyngitis (16.1%), headache (12.6%), and cough (12.6%).

Table 28. Adverse events that occurred in patients in any treatment group

System Organ Class / Preferred Term	Tamsulosin Dose Group			
	Low	Medium	High	Total
Total number of patients receiving dose at any time	82	61	41	87
Total with adverse events	51 (62.2)	26 (42.6)	33 (80.5)	79 (90.8)
Infections and infestations	**27 (32.9)**	**18 (29.5)**	**26 (63.4)**	**59 (67.8)**
Urinary tract infection	15 (18.3)	11 (18.0)	16 (39.0)	36 (41.4)
Pharyngitis	11 (13.4)	1 (1.6)	2 (4.9)	14 (16.1)
Nasopharyngitis	4 (4.9)	3 (4.9)	1 (2.4)	7 (8.0)
Cervicitis	1 (1.2)	0 (0.0)	3 (7.3)	4 (4.6)
Upper respiratory tract infection	1 (1.2)	1 (1.6)	3 (7.3)	5 (5.7)
Influenza	3 (3.7)	1 (1.6)	1 (2.4)	5 (5.7)
Gastroenteritis	2 (2.4)	0 (0.0)	2 (4.9)	4 (4.6)
Nervous system disorders	**10 (12.2)**	**3 (4.9)**	**5 (12.2)**	**16 (18.4)**
Headache	8 (9.8)	2 (3.3)	3 (7.3)	11 (12.6)
Dizziness	3 (3.7)	1 (1.6)	1 (2.4)	5 (5.7)
Vascular disorders	**2 (2.4)**	**2 (3.3)**	**1 (2.4)**	**5 (5.7)**
Orthostatic hypotension[a]	1 (1.2)	2 (3.3)	1 (2.4)	4 (4.6)
Respiratory, thoracic and mediastinal disorders	**11 (13.4)**	**2 (3.3)**	**7 (17.1)**	**20 (23.0)**
Cough	7 (8.5)	1 (1.6)	3 (7.3)	11 (12.6)
Oropharyngeal pain	3 (3.7)	0 (0.0)	1 (2.4)	4 (4.6)
Gastrointestinal disorders	**24 (29.3)**	**8 (13.1)**	**8 (19.5)**	**38 (43.7)**
Vomiting	9 (11.0)	4 (6.6)	3 (7.3)	15 (17.2)
Diarrhoea	4 (4.9)	2 (3.3)	2 (4.9)	8 (9.2)
Nausea	4 (4.9)	2 (3.3)	0 (0.0)	6 (6.9)
Abdominal pain	4 (4.9)	0 (0.0)	1 (2.4)	5 (5.7)
Abdominal pain upper	3 (3.7)	1 (1.6)	1 (2.4)	5 (5.7)
Renal and urinary disorders	**7 (8.5)**	**2 (3.3)**	**5 (12.2)**	**14 (16.1)**
Hydronephrosis	2 (2.4)	1 (1.6)	3 (7.3)	6 (6.9)
General disorders and administration site conditions	**18 (22.0)**	**3 (4.9)**	**7 (17.1)**	**26 (29.9)**
Pyrexia	12 (14.6)	3 (4.9)	6 (14.6)	20 (23.0)

Percentages are calculated based on total number of patients per treatment as the denominator; patients may be counted in more than one dose group (due to titration for efficacy).
a Occurred during orthostatic testing; sponsor requested that these declines in SBP are reported as adverse events.
System organ class totals include all adverse events that occurred within that organ class.
Source: Table 15.3.2.2: 1

Most patients showed either improvement or stabilization of hydroureter (88.5% right kidney; 85.9% left kidney) and hydronephrosis (88.5% right kidney; 82.1% left kidney) at week 52 when compared to baseline. A dose dependent response is not expected since most subjects (~93%) enrolled had normal or Grade I hydronephrosis at baseline.

Table 29. Summary of improvement or stabilization of US renal evaluation by dose group

	Tamsulosin Dose Group			
	Low N (%)	Medium N (%)	High N (%)	Total N (%)
Number of patients	27	17	34	78
Hydroureter[a]				
Right Kidney	26 (96.3)	15 (88.2)	28 (82.4)	69 (88.5)
Left Kidney	24 (88.9)	14 (82.4)	29 (85.3)	67 (85.9)
Hydronephrosis[b]				
Right Kidney	26 (96.3)	15 (88.2)	28 (82.4)	69 (88.5)
Left Kidney	24 (88.9)	14 (82.4)	26 (76.5)	64 (82.1)

Patients are classified according to the treatment they were receiving at Week 52 or end of treatment.
a Hydroureter response is defined as improvement or stabilization based upon the presence or absence of hydroureter at end of treatment compared to baseline.
b Hydronephrosis response is defined as an improvement or stabilization based upon ultrasound grading at the end of the study. The lower or same grade at end of treatment compared to baseline is considered an improvement or stabilization.
Source: Table 15.2.3.1: 1

7.2.2.2 Postmarketing experience

Postmarketing experience with tamsulosin HCl in the pediatric population is limited since tamsulosin HCl is not presently approved for use in children by the Agency.

7.2.2.3 Literature

None

7.2.3 Adequacy of Overall Clinical Experience

There is adequate clinical data in the pivotal trial to assess the efficacy and safety of tamsulosin HCl for the reduction of detrusor leak point pressure in children age 2-16 with neuropathic bladders. While there were an insufficient number of Black and Hispanic patients in this study to draw any conclusions about safety and efficacy in these subpopulations, it is this medical officer's opinion that it is reasonable to assume both safety and efficacy in those

populations as there is no current evidence to suggest race specific differences in safety and efficacy for alpha adrenergic antagonists.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special animal and/or *in vitro* testing had been previously reviewed and found acceptable. The reader is referred to the Pharmacologist's review for a description of the juvenile monkey study and its results.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing was adequate given the prior experience with this drug.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This information had been previously reviewed and found acceptable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events associated with the use of tamsulosin HCl have been well characterized with this and previous alpha adrenergic antagonists. Alpha adrenergic antagonists are associated with small but increased risks of postural hypotension, dizziness, syncope, and vertigo. Serious cases of postural hypotension, syncope, or cardiac arrhymias were not seen in the pivotal randomized Study BI 527.51 nor in the long term open-label safety Study BI 527.66.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted and reviewed was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

In October 2009, a safety update summarizing the extended safety data of patients rolled over from the pivotal Phase 3 study BI-527.51 was submitted. Group D-Rollover portion of the BI-527.66 study was terminated early based on the 527.51 data which showed lack of efficacy. Of the 105 Rollover patients who were screened, 96 patients were entered in the extended safety study and all were treated. Two patients completed study treatment prior to the early termination

of the BI-527.66 study. Two patients discontinued treatment due to adverse events and the remaining 92 (95.8%) patients discontinued treatment due to the early termination of the study. Since limited data was collected due to early trial termination and there was variation in treatment duration across patients, efficacy variables were not analyzed according to protocol.

Overall, the mean duration of tamsulosin HCl treatment in the extended rollover phase of study was 106 days. Over a third of the patients (36.5%) completed 29 to 60 days of treatment; 18.8% of patients completed 91 to 180 days of tamsulosin HCl treatment prior to the termination of the study.

Table 30. Exposure to study medication by last value on treatment.

	Tamsulosin Dose Group			
	Low	**Medium**	**High**	**TOTAL**
Duration of treatment, days				
Number of patients	54	13	29	96
Mean	122.33	89.62	82.90	105.99
SD	90.42	110.39	70.04	88.87
Min	7.0	12.0	23.0	7.0
Median	85.50	53.00	58.00	67.00
Max	367.0	367.0	290.0	367.0
Duration of treatment, N (%)				
1 to 7 days	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.0)
8 to 14 days	0 (0.0)	2 (15.4)	0 (0.0)	2 (2.1)
15 to 21 days	0 (0.0)	1 (7.7)	0 (0.0)	1 (1.0)
22 to 28 days	0 (0.0)	1 (7.7)	3 (10.3)	4 (4.2)
29 to 60 days	15 (27.8)	6 (46.2)	14 (48.3)	35 (36.5)
61 to 90 days	12 (22.2)	0 (0.0)	6 (20.7)	18 (18.8)
91 to 180 days	15 (27.8)	1 (7.7)	2 (6.9)	18 (18.8)
181 to 270 days	4 (7.4)	0 (0.0)	3 (10.3)	7 (7.3)
>= 271 days	7 (13.0)	2 (15.4)	1 (3.4)	10 (10.4)

Patients are classified according to the treatment they were taking at their last value on treatment.
Percentages may total greater than 100% due to rounding.
Exposure durations include 3 day washout period.
Source: Table 15.3.1.1: 1

A total of 43 (44.8%) patients reported adverse events while receiving tamsulosin HCl during the study (48.1% low, 38.5% medium, 41.4% high). Overall, few patients experienced adverse events that were considered related to study medication (4.2%) or resulted in discontinuation of treatment (3.1%); no patients treated with the low dose of tamsulosin HCl had related, severe, or

discontinuations due to adverse events. Only 3 patients experienced serious adverse events (SAE) during the study (one patient per treatment group). No deaths occurred during the study.

Table 31. Overall summary of adverse events by dose at the last on-treatment visit

	Tamsulosin Dose Group			
	Low N (%)	Medium N (%)	High N (%)	TOTAL N (%)
Number of patients	54	13	29	96
Patients with any AEs	26 (48.1)	5 (38.5)	12 (41.4)	43 (44.8)
Patients with severe AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with investigator defined drug-related AEs	0 (0.0)	2 (15.4)	2 (6.9)	4 (4.2)
Patients with other significant AEs (according to ICH E3)	0 (0.0)	1 (7.7)	0 (0.0)	1 (1.0)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	2 (15.4)	1 (3.4)	3 (3.1)
Patients with significant AEs (pre-specified events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious AEs	1 (1.9)	1 (7.7)	1 (3.4)	3 (3.1)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Required hospitalisation	1 (1.9)	1 (7.7)	0 (0.0)	2 (2.1)
Prolonged hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.0)

A patient may be counted in more than one seriousness criterion
Percentages are calculated using total number of patients per treatment as the denominator
MedDRA version used for reporting: 11.1
Other Significant Adverse event: All adverse events that are marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a intervention
Source: Table 15.3.2.1: 2

There did not appear to be a consistent relationship between dose and incidence of adverse events. Urinary tract infection continued to be reported more frequently in patients treated with high-dose tamsulosin HCl (24.1%), which may reflect the difficulty in treating those patients with the highest LPP. Of the most frequently reported Gastrointestinal adverse events (vomiting, abdominal pain, and diarrhea), only abdominal pain was reported more often in patients at the highest dose of tamsulosin HCl.

Table 32. Adverse events reported in at least 3% of patients (total) by dose at the last on-treatment visit

	Tams-low N (%)	Tams-medium N (%)	Tams-high N (%)	Total N (%)
Number of patients	54	13	29	96
Total with adverse events	26 (48.1)	5 (38.5)	12 (41.4)	43 (44.8)
Infections and infestations	**20 (37.0)**	**4 (30.8)**	**9 (31.0)**	**33 (34.4)**
Urinary tract infection	9 (16.7)	2 (15.4)	7 (24.1)	18 (18.8)
Nasopharyngitis	5 (9.3)	1 (7.7)	2 (6.9)	8 (8.3)
Influenza	5 (9.3)	0 (0.0)	0 (0.0)	5 (5.2)
Gastroenteritis	2 (3.7)	2 (15.4)	0 (0.0)	4 (4.2)
Pharyngitis	2 (3.7)	0 (0.0)	2 (6.9)	4 (4.2)
Nervous system disorders	**2 (3.7)**	**1 (7.7)**	**2 (6.9)**	**5 (5.2)**
Headache	2 (3.7)	0 (0.0)	2 (6.9)	4 (4.2)
Gastrointestinal disorders	**5 (9.3)**	**3 (23.1)**	**5 (17.2)**	**13 (13.5)**
Vomiting	2 (3.7)	2 (15.4)	1 (3.4)	5 (5.2)
Diarrhoea	1 (1.9)	2 (15.4)	0 (0.0)	3 (3.1)
Abdominal pain	0 (0.0)	0 (0.0)	3 (10.3)	3 (3.1)
General disorders and administration site conditions	**1 (1.9)**	**1 (7.7)**	**2 (6.9)**	**4 (4.2)**
Pyrexia	0 (0.0)	1 (7.7)	2 (6.9)	3 (3.1)

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 11.1
Source: Table 15.3.2.2: 7

Three patients experienced SAEs during the study. Narratives for these patients were reviewed which reflect infectious complications of pneumonia, complicated UTI, and gastroenteritis. All required hospitalization for treatment and recovered from the acute clinical episode. The SAEs are not considered related to study medication and likely reflect the chronic debilitating effects of the primary neurological disorder and altered genitourinary physiology.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most frequently reported AE of urinary tract infections is a likely sequalae of clean intermittent catheterization, which is the primary management of neuropathic bladders in children with myelomeningocele. GI disorders are also common in this group of neurologically impaired children and increased frequency of upper respiratory tract infections is expected in children. These common AEs were distributed across all treatment groups and likely reflect the unique patient population enrolled into study.

Overall, there was a low occurrence of orthostatic hypotension and the few incidences recorded were balanced between the placebo and active treatment groups. Serious cases of postural hypotension, syncope, or cardiac arrhythmias were not seen in the pivotal randomized Study BI 527.51 nor in the long term open-label safety Study BI 527.66.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The safety data from studies 527.51 and 527.66 were pooled and analyzed. The safety analysis primarily focused on the comparison between the tamsulosin total group and the placebo group.

Table 33. Adverse Overall summary of adverse events – pooled analysis
(treated set - treatment at onset)

	Placebo N=41 n (%)	Tamsulosin total N=207 n (%)
Patients with any AE	18 (43.9)	146 (70.5)
Patients with any severe AEs	2 (4.9)	12 (5.8)
Patients with any drug-related AEs	2 (4.9)	15 (7.2)
Patients with other significant AEs (according to ICH E3)	1 (2.4)	7 (3.4)
Patients with any AE leading to discontinuation from the study	1 (2.4)	8 (3.9)
Patients with SAEs	1 (2.4)	10 (4.8)
Deaths	0	1 (0.5)
Immediately life-threatening	0	1 (0.5)
Requires hospitalization	1 (2.4)	9 (4.3)
Prolongs hospitalization	0	1 (0.5)
Other	0	1 (0.5)

Note: a patient could be counted in more than 1 seriousness criterion
AEs were classified according to treatment at onset

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

More patients in the tamsulosin total group reported drug-related AEs (7.2% versus 4.9% in the placebo group). The difference was primarily due to a higher incidence of dizziness and hypotension attributed to treatment in the tamsulosin group. When the frequency of AEs was analyzed by tamsulosin dose group, it was observed that in the tamsulosin high dose group more patients reported adverse events (59.3%) and SAEs (4.9%) than in the tamsulosin low (44.6% and 1.5%, respectively), and medium (35.5% and 2.1%, respectively) dose groups.

The only SAEs reported in more than 1 patient were urinary tract infections (reported in 2 patients in the tamsulosin group and 0 patients in the placebo group), hydrocephalus (reported in 3 patients in the tamsulosin group and 0 patients in the placebo group), and ventriculoperitoneal shunt malfunction (reported in 2 patients in the tamsulosin group and 0 patients in the placebo group). None of the SAEs were considered related to the study drug.

Table 34. Adverse Overview of serious adverse events, sorted by decreasing frequency in the tamsulosin group:

Preferred term	Placebo N=41 n (%)	Tamsulosin total N=207 n (%)
Patients with any SAE	1 (2.4)	10 (4.8)
Hydrocephalus	0	3 (1.4)
Urinary tract infection	0	2 (1.0)
Ventriculoperitoneal shunt malfunction	0	2 (1.0)
Tethered cord syndrome	0	1 (0.5)
Cellulitis	0	1 (0.5)
Dengue fever	0	1 (0.5)
Asthma	0	1 (0.5)
Peritoneal cyst	0	1 (0.5)
Tibial torsion	0	1 (0.5)
Death	0	1 (0.5)
Shunt malfunction	1 (2.4)	0
Haematoma	1 (2.4)	0

AEs were classified according to treatment at onset

7.4.2.2 Explorations for time dependency for adverse findings

The overall mean duration of tamsulosin treatment based on the pooled safety database was 195.2 days, with a range from 3 to 422 days. The mean duration of placebo treatment was shorter with 99.6 days (range 34 to 126 days), reflecting the fact that placebo was only used in the 527.51 study which had a planed study duration of 14 weeks.

Table 35. Duration of treatment

Study	FDA requirements					Actual enrolment				
	Placebo	Low dose	Medium dose	High dose	Total	Placebo	Low dose	Medium dose	High dose	Total
Study 527.51	30	30	30	30	120	41	40	39	41	161
Study 527.66										
PK population	NA	9	9	9	27	NA	10	9	10	29
Treated population[a]	NA	NS	NS	NS	NS	NA	29	21	37	87
6 months exposure[a]	NA	NS	NS	NS	75	NA	27	16	34	77
12 months exposure[a]	NA	NS	NS	NS	50	NA	27	16	31	73
Total in both studies	30	NS	NS	NS	NS	41	69	60	78	248

NS = not specified; NA = not applicable
[a] Includes both PK and de-novo patients from study 527.66

Titration periods were utilized in both study protocols, hence the longest exposure was observed for the lowest dose groups. Considering this study design and low levels of SAEs, no firm relationship regarding time dependency of AEs is noted.

7.4.2.3 Explorations for drug-demographic interactions

The longest mean treatment duration was observed in the youngest patient group (208 days). In the placebo group, the mean exposure was similar in all age groups, but a shorter exposure was seen with increasing age in the tamsulosin total group.

Table 36. Duration of treatment by age

Overall duration of treatment	Placebo	Tamsulosin total
Age group (years)		
2 to <5 years	7	45
Mean (SD) [days]	101.86 (3.02)	207.91 (134.61)
Overall patient years	2.0	25.6
5 to <10 years	18	90
Mean (SD) [days]	99.94 (17.82)	201.01 (136.52)
Overall patient years	4.9	49.5
10 to 16 years	16	72
Mean (SD) [days]	98.31 (14.58)	179.97 (124.46)
Overall patient years	4.3	35.5

Mean duration of treatment was longer for female patients in the tamsulosin total group (212 days) than in males (182 days). In the placebo group, no notable difference was seen between the 2 subgroups.

Table 37. Duration of treatment by sex

Overall duration of treatment	Placebo	Tamsulosin total
Sex		
Male	25	117
Mean (SD) [days]	100.24 (12.23)	182.15 (128.78)
Overall patient years	6.9	58.3
Female	16	90
Mean (SD) [days]	98.69 (18.43)	212.14 (134.64)
Overall patient years	4.3	52.3

Source data: Module 5.3.5.3, Table 1.1.5

7.4.2.4 Explorations for drug-disease interactions

ECG recordings revealed overall that 8.2% of patients in the tamsulosin total group and 14.6% of patients in the placebo group had normal results at baseline but abnormal readings at the end of the study. The most common changes were related to cardiac rhythm (14.6% of patients in the placebo group and 15.5% in the tamsulosin total group). Only 3 patients had cardiac AEs: palpitations of moderate intensity in a patient treated with tamsulosin low dose, tachycardia of mild intensity reported in a patient treated with tamsulosin low dose, and sinus tachycardia of mild intensity in a patient treated with tamsulosin high dose. The only event considered to be drug-related was the palpitations. These results indicate that tamsulosin does not have an adverse effect on cardiac function.

Visual acuity tests were summarized at baseline and the final visit to identify any potential deterioration over the treatment period. At the last value on treatment, 13.0% patients in the tamsulosin and 14.6% patients in the placebo group had a decrease in visual acuity in their right eye, and 14.5% patients in the tamsulosin group and 9.8% patients in the placebo group had a decrease in visual acuity in their left eye. This was compared to 20.8% patients in the tamsulosin group and 9.8% patients in the placebo group who had an increase in visual acuity in their right eye and 22.7% patients in the tamsulosin group and 12.2% patients in the placebo group who had an increase in visual acuity in their left eye. No consistent changes were noted to suggests that tamsulosin has an adverse effect on visual acuity in this patient population.

7.4.2.5 Explorations for drug-drug interactions

Concomitant anticholinergic medication was utilized in 34.6% of the patients in the pooled treated patient population. Overall AEs were comparable between the subgroups who had been receiving anti-cholinergic medications in the tamsulosin total group (74%) and the group who had not been receiving anti-cholinergic medications (69%). More severe AEs were seen for the subgroup who had not been receiving anti-cholinergic medications in the tamsulosin total group (7.3%) than the group who had been receiving anti-cholinergic medications (2.9%). However, drug related AEs were higher in the subgroup who had been receiving anti-cholinergic medications in the tamsulosin total group (13%) than the group who had not been receiving anti-

cholinergic medications (4.4%). No notable changes in severe or serious AE profile were seen by whether patients were receiving concomitant anti-cholinergics or not.

7.4.3 Causality Determination

None

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Tamsulosin drug substance used to manufacture the tamsulosin capsules used in the pediatric clinical trials was identical to that used in the commercial Flomax® capsules (as per NDA 20-579). In both studies (527.51 and 527.66), tamsulosin was to be administered once daily, in dosages of 0.025 mg, 0.05 mg, 0.1 mg, 0.2 mg, or 0.4 mg, 30 minutes after breakfast, with the contents of the capsules being sprinkled over a teaspoon of apple sauce or yogurt, followed by a spoonful of water. A precise mg/kg-based dosing scheme was not possible due to the modified-release formulation characteristics of tamsulosin capsules.

8.2 Drug-Drug Interactions

No new drug interaction studies were submitted in this application.

8.3 Special Populations

No patients with hepatic insufficiency or renal insufficiency (creatinine clearance < 30 mL/min) were included in this submission.

8.4 Pediatrics

The clinical studies submitted in this application involved only pediatric patients age 2-16.

8.5 Advisory Committee Meeting

There was no need for an advisory committee meeting to evaluate this NDA submission.

8.6 Literature Review

None

8.7 Postmarketing Risk Management Plan

No risk management plan was submitted and no specific safety concern for which a risk management plan would be necessary was identified.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Pivotal trial BI 527.51 does not support the efficacy of daily dosing of oral tamsulosin HCl for the reduction of detrusor leak point pressure in children with neuropathic bladders. The available data is consistent with a lack of an efficacy effect on both primary and secondary endpoints. It is recommended that this new indication and dosing regimen not be incorporated into the current PI. However, the study description and efficacy evaluations should be conveyed in the PI.

The safety profile of tamsulosin in children is consistent with the alpha adrenergic antagonist class. Adverse events identified in children using tamsulosin are reflective of the underlying neurological disorder resulting in neuropathic bladders.

9.2 Recommendation on Regulatory Action

With minor modifications to the Sponsor's proposed labeling, the application may be approved..

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

Under "USE IN SPECIFIC POPULATIONS" section and "Pediatric Use" subsection, the Sponsor proposes to insert the following:

(b) (4)

The proposed labeling change is reflective of safety and efficacy data available in the current sNDA submission.

9.5 Comments to Applicant

None

10 Appendices

None

REFERENCES

None

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/

CHONG M KIM
11/25/2009

MARK S HIRSCH
11/25/2009
I concur.