



## Clinical trial results:

**An uncontrolled, open-label, titration, long-term safety (up to 12 months) and efficacy study of tamsulosin hydrochloride in children with neuropathic bladder, with a randomized pharmacokinetic sub-study investigating low, medium and high dose ranges.**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-004423-11 |
| Trial protocol           | DE IT BE ES    |
| Global end of trial date | 30 June 2009   |

## Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 23 July 2016  |
| First version publication date | 01 August 2015  |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Data correction due to a system error in EudraCT- Results |

## Trial information

### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 527.66 |
|-----------------------|--------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00340704 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Boehringer Ingelheim   |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216   |
| Public contact               | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a> |
| Scientific contact           | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a> |

Notes:

## Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

|  |     |
|--|-----|
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
|--|-----|

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 23 October 2009 |
| Is this the analysis of the primary completion data? | No              |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 30 June 2009 |
| Was the trial ended prematurely? | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

To characterise the pharmacokinetic (PK)/ pharmacodynamic (PD) profile and evaluate the safety and efficacy of tamsulosin hydrochloride (HCL) in children with an elevated detrusor leak point pressure associated with a known neurological disorder (e.g. spinal bifida), after which long-term safety can be assessed.

This trial has 3 different Data base locks (DBL) based on three separate populations PK / PD, Group D – Denovo and Group D – 527.51 Rollover. For PK / PD population the DBL date was 18July2007, for Group D – Denovo population the DBL date was 23Jan2009 and for Group D – 527.51 Rollover population the DBL date was 11Sep2009.

The Group D-Rollover portion of Study 527.66 was terminated early based on data from placebo-controlled Study 527.51 that showed lack of efficacy, thus, caution should be used in interpreting these results due to the impact of the early termination, as well as the impact of the study design on interpretation of results by dose.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

|   |               |
|---|---------------|
| Evidence for comparator: -                                |               |
| Actual start date of recruitment                          | 19 April 2006 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 5          |
| Country: Number of subjects enrolled | Italy: 6          |
| Country: Number of subjects enrolled | India: 26         |
| Country: Number of subjects enrolled | United States: 58 |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Mexico: 53             |
| Country: Number of subjects enrolled | Russian Federation: 5  |
| Country: Number of subjects enrolled | Korea, Republic of: 18 |
| Country: Number of subjects enrolled | South Africa: 14       |
| Country: Number of subjects enrolled | Ukraine: 13            |
| Country: Number of subjects enrolled | Philippines: 51        |
| Country: Number of subjects enrolled | Brazil: 22             |
| Country: Number of subjects enrolled | Canada: 5              |
| Country: Number of subjects enrolled | Germany: 8             |
| Worldwide total number of subjects   | 284                    |
| EEA total number of subjects         | 19                     |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 226 |
| Adolescents (12-17 years)                 | 58  |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This trial has 3 different DBLs and 3 different Clinical trial reports which were prepared based on 3 separate populations PK/PD, Group D-Denovo and Group D-527.51 Rollover. Group D-Denovo includes subjects from PK Phase and additional subjects and Group D – 527.51 Rollover includes subjects who successfully completed tamsulosin HCl Study 527.51.

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | PK sub-study (Treatment period) |
| Is this the baseline period? | No                              |
| Allocation method            | Not applicable                  |
| Blinding used                | Not blinded                     |

Blinding implementation details:

This was an open label, randomised and uncontrolled study.

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | tamsulosin - low dose level (Steady State - PK study) |

Arm description:

Subjects randomized to low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the Leak point pressure (LPP) results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received low dose of 0.025 mg qd (once daily), body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | tamsulosin hydrochloride (0.025 mg) |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Capsule                             |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Subjects randomized to low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride and body weight of 12.1–25.0 kg received low dose of 0.025 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects randomized to low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride and body weight of 25.1–50.0 kg received low dose of 0.05 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects randomized to low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                  |  |
|------------------|--|
| <b>Arm title</b> | tamsulosin - medium dose level (Steady State - PK study) |
|------------------|--|

Arm description:

Subjects randomized to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the LPP results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received medium dose of 0.05 mg qd, body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd with and body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects randomized to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 12.1–25.0 kg received medium dose of 0.05 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects randomized to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.2 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects randomized to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                  |  |
|------------------|--|
| <b>Arm title</b> | tamsulosin - high dose level (Steady State - PK study) |
|------------------|--|

**Arm description:**

Subjects randomized to high dose level(0.004-0.008mg/kg) of tamsulosin hydrochloride,dependent on a subject's body weight.In PK study,all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight.Depending on the results of the LPP,subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy. Subjects with body weight of 12.1-25.0kg received high dose of 0.1mg qd, body weight of 25.1-50.0kg received high dose of 0.2mg qd & body weight of 50.1-100.0kg received high dose of 0.4mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.One subject randomised to high dose level was not treated. Although actual number of subjects started is 11,10 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

**Dosage and administration details:**

Subjects randomized to high dose level (0.004-0.008mg/kg) of tamsulosin hydrochloride and body weight of 12.1-25.0 kg received high dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.2 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

**Dosage and administration details:**

Subjects randomized to high dose level (0.004-0.008mg/kg) of tamsulosin hydrochloride and body weight of 25.1–50.0 kg received high dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.4 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

**Dosage and administration details:**

Subjects randomized to high dose level (0.004-0.008mg/kg) of tamsulosin hydrochloride and body weight of 50.1–100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

| <b>Number of subjects in period 1</b> | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |
|---------------------------------------|---|--|--|
| Started                               | 10  | 10   | 10   |
| Completed                             | 10  | 9  | 10   |
| Not completed                         | 0   | 1  | 0  |
| Adverse event, non-fatal              | -   | 1  | -  |

**Period 2**

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 2 title               | Group D-Denovo (Treatment period) |
| Is this the baseline period? | No                                |
| Allocation method            | Not applicable                    |
| Blinding used                | Not blinded                       |

Blinding implementation details:

Open-label, uncontrolled trial and dose titrated, starting at the lowest dose level based on a subject's weight, in order to establish their individual efficacious dose.

**Arms**

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | No   |
| <b>Arm title</b>             | tamsulosin - low dose level (Group D-Denovo) |

Arm description:

Subjects received low dose level (0.001 – 0.002 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 12.1– 25.0 kg received low dose of 0.025 mg qd, body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | tamsulosin hydrochloride (0.025 mg) |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Capsule                             |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Subjects with body weight of 12.1– 25.0 kg received low dose of 0.025 mg qd of tamsulosin hydrochloride by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects with body weight of 25.1–50.0 kg received low dose of 0.05 mg qd of tamsulosin hydrochloride by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects with body weight of 50.1–100.0 kg received low dose of 0.1 mg qd of tamsulosin hydrochloride by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                  |   |
|------------------|---|
| <b>Arm title</b> | tamsulosin - medium dose level (Group D-Denovo) |
|------------------|---|

Arm description:

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 9.0–12.0 kg received medium dose of 0.025 mg qd as their starting dose, body weight of 12.1–25.0 kg could have titrated to a medium dose of 0.05 mg qd, body weight of 25.1–50.0 kg could have titrated to a medium dose of 0.1 mg qd and body weight of 50.1–100.0 kg could have titrated to a medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | tamsulosin hydrochloride (0.025 mg) |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Capsule                             |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Subjects received medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 9.0–12.0 kg received medium dose of 0.025 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 12.1–25.0 kg received medium dose of 0.05 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.2 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                  |   |
|------------------|---|
| <b>Arm title</b> | tamsulosin - high dose level (Group D-Denovo) |
|------------------|---|

Arm description:

Subjects titrated to high dose level (0.004–0.008 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the



children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 9.0-12.0 kg received high dose of 0.05 mg qd, body weight of 12.1-25.0 kg received high dose of 0.1 mg qd, body weight of 25.1-50.0 kg received high dose of 0.2 mg qd & body weight of 50.1-100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 9.0–12.0 kg received high dose of 0.05 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 12.1–25.0 kg received high dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.2 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 25.1–50.0 kg received high dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.4 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 50.1–100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

| Number of subjects in period 2           | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-Denovo) |
|--|--|---|---|
| Started                                  | 29   | 21  | 37  |
| PK Study Subjects Entered Group D-Denovo | 7 <sup>[1]</sup>                             | 5 <sup>[2]</sup>                                | 18 <sup>[3]</sup>                             |
| Completed                                | 27   | 16  | 30  |
| Not completed                            | 2  | 5   | 7   |
| Other reason not defined above           | -  | -   | 3   |
| Consent withdrawn by subject             | -  | 1   | 3   |
| Adverse event, non-fatal                 | 2  | 4   | -   |
| Protocol deviation                       | -  | -   | 1   |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Three different Clinical trial reports were prepared based on 3 separate populations (PK/PD, Group D-Denovo & Group D-527.51). Group D-Denovo includes patients from PK Phase & additional subjects. Thus this milestone represents the number of PK Study Subjects who Entered Group D-Denovo and treated for tamsulosin - low dose level.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Three different Clinical trial reports were prepared based on 3 separate populations (PK/PD, Group D-Denovo & Group D-527.51). Group D-Denovo includes patients from PK Phase & additional subjects. Thus this milestone represents the number of PK Study Subjects who Entered Group D-Denovo and treated for tamsulosin - medium dose level.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Three different Clinical trial reports were prepared based on 3 separate populations (PK/PD, Group D-Denovo & Group D-527.51). Group D-Denovo includes patients from PK Phase & additional subjects. Thus this milestone represents the number of PK Study Subjects who Entered Group D-Denovo and treated for tamsulosin - high dose level.

### Period 3

|                              |                                     |
|------------------------------|-------------------------------------|
| Period 3 title               | Group D-Rollover (Treatment period) |
| Is this the baseline period? | Yes <sup>[4]</sup>                  |
| Allocation method            | Not applicable                      |
| Blinding used                | Not blinded                         |

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | No  |
| <b>Arm title</b>             | tamsulosin - low dose level (Group D-527.51 Rollover) |

Arm description:

Subjects received low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D- 527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial (527.66). All subjects were to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that that the higher doses would provide some efficacy.

Subjects with body weight of 12.1-25.0 kg received low dose of 0.025 mg qd, body weight of 25.1-50.0 kg received low dose of 0.05 mg qd and body weight of 50.1-100.0 kg qd received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                                     |
|--|-------------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.025 mg) |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Capsule                             |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Subjects with body weight of 12.1– 25.0 kg received low dose of 0.025 mg qd of tamsulosin hydrochloride by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects with body weight of 25.1–50.0 kg received low dose of 0.05 mg qd of tamsulosin hydrochloride by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects with body weight of 50.1–100.0 kg received low dose of 0.1 mg qd of tamsulosin hydrochloride by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                  |  |
|------------------|--|
| <b>Arm title</b> | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|------------------|--|

Arm description:

Subjects who were to receive medium dose level (0.002-0.004 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial. All subjects were to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that the higher doses would provide some efficacy.

Subjects with body weight of 9.0-12.0 kg received medium dose of 0.025 mg qd, body weight of 12.1-25.0 kg received medium dose of 0.05 mg qd, body weight of 25.1-50.0 kg received medium dose of 0.1 mg qd, body weight of 50.1-100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | tamsulosin hydrochloride (0.025 mg) |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Capsule                             |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Subjects received medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 9.0–12.0 kg received medium dose of 0.025 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

**Dosage and administration details:**

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 12.1–25.0 kg received medium dose of 0.05 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

**Dosage and administration details:**

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.2 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

**Dosage and administration details:**

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride and body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                  |  |
|------------------|--|
| <b>Arm title</b> | tamsulosin - high dose level (Group D-527.51 Rollover) |
|------------------|--|

**Arm description:**

Subjects titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial. All subjects had to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that the higher doses would provide some efficacy.

Subjects with body weight of 9.0-12.0 kg received high dose of 0.05 mg, body weight of 12.1-25.0 kg received high dose of 0.1 mg, body weight of 25.1-50.0 kg received high dose of 0.2 mg, body weight of 50.1-100.0 kg received high dose of 0.4 mg by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                    |
|--|------------------------------------|
| Arm type                               | Experimental                       |
| Investigational medicinal product name | tamsulosin hydrochloride (0.05 mg) |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Capsule                            |
| Routes of administration               | Oral use                           |

**Dosage and administration details:**

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 9.0–12.0 kg received high dose of 0.05 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.1 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

**Dosage and administration details:**

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 12.1–25.0 kg received high dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.2 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 25.1–50.0 kg received high dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | tamsulosin hydrochloride (0.4 mg) |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule                           |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Subjects who were titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride and body weight of 50.1–100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

Notes:

[4] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Three separate reports were prepared for this study evaluating 3 different populations: PK sub-study, Group D-Denovo and the Group D Rollover (included subjects who entered Study 527.66 from Study 527.51). Since period 1 evaluates only the PK sub-study population, Group D-Rollover baseline data information was selected to be used for this evaluation.

| <b>Number of subjects in period 3</b> | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |
|---------------------------------------|---|--|--|
| Started                               | 54  | 13   | 29   |
| Completed                             | 1   | 1  | 0  |
| Not completed                         | 53  | 12   | 29   |
| Other reason not defined above        | 53  | 11   | 28   |
| Adverse event, non-fatal              | -   | 1  | 1  |

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Group D-Rollover (Treatment period) |
|-----------------------|-------------------------------------|

Reporting group description: -

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on the subjects who were randomised after successfully completing the screening period and received at least one dose of the trial medication (Group D-Rollover).

| Reporting group values | Group D-Rollover<br>(Treatment period) | Total |  |
|------------------------|--|-------|--|
| Number of subjects     | 96                                     | 96    |  |
| Age categorical        |  |       |  |
| Units: Subjects        |  |       |  |

|  |       |    |  |
|--|-------|----|--|
| Age continuous   |       |    |  |
| Treated Set: Includes all patients who are dispensed study medication and are documented to have taken at least one dose of treatment. In this study, some of the subjects are in multiple phases: PK and Group D-Denovo. Thus, the baseline characteristics are based on the unique subject entered into the study. |       |    |  |
| Units: years   |       |    |  |
| arithmetic mean  | 8     |    |  |
| standard deviation   | ± 3.8 | -  |  |
| Gender categorical   |       |    |  |
| Units: Subjects  |       |    |  |
| Female   | 41    | 41 |  |
| Male   | 55    | 55 |  |

### Subject analysis sets

|                            |   |
|----------------------------|---|
| Subject analysis set title | PK Study - Single dose (Treatment period) |
|----------------------------|---|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The subject analysis type is infact Pharmacokinetics single dose set (PK-SD).

Subjects received low dose level (0.001 – 0.002 mg/kg) of tamsulosin hydrochloride once daily dependent on a subject's body weight (12.1 – 25.0 kg, 25.1 – 50.0 kg and 50.1 – 100.0 kg), by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

All subjects who were randomized, successfully took and retained the first dose of study medication and provided blood samples for PK after single dose were included in the PK-SD set.

In PK Single dose study, it was planned to obtain the Low dose PK data after single dose from all the 30 patients randomized to Low, Medium and high. However as per the protocol amendment, the PK sampling after first drug administration of low dose level was stopped after inclusion of 11 patients and therefore the PK sample of 11 patients were evaluated for PK single dose.

|                            |  |
|----------------------------|--|
| Subject analysis set title | PK Study - Steady state (Treatment period) |
|----------------------------|--|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The subject analysis type is infact pharmacokinetics steady state set (PK-SS).

In PK study - steady state, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the Leak point pressure (LPP)

results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

pharmacokinetics steady state set (PK-SS): Includes all subjects who were randomized successfully took study medication for two weeks at their randomized dose level and provided blood samples for PK at their steady state visit were included in the PK-SS set.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | D-Denovo (Treatment Period) |
| Subject analysis set type  | Intention-to-treat          |

Subject analysis set description:

The subject analysis type is in fact Treated set.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Treated set (Treat): Includes all subjects who are dispensed study medication and are documented to have taken at least one dose of treatment.

| Reporting group values             | PK Study - Single dose (Treatment period) | PK Study - Steady state (Treatment period) | D-Denovo (Treatment Period) |
|------------------------------------|---|--|-----------------------------|
| Number of subjects                 | 11  | 29   | 87                          |
| Age categorical<br>Units: Subjects |   |  |                             |

|  |       |       |       |
|--|-------|-------|-------|
| Age continuous   |       |       |       |
| Treated Set: Includes all patients who are dispensed study medication and are documented to have taken at least one dose of treatment. In this study, some of the subjects are in multiple phases: PK and Group D-Denovo. Thus, the baseline characteristics are based on the unique subject entered into the study. |       |       |       |
| Units: years   |       |       |       |
| arithmetic mean  | 6.5   | 8     | 7.4   |
| standard deviation   | ± 4.3 | ± 3.8 | ± 3.7 |
| Gender categorical<br>Units: Subjects  |       |       |       |
| Female   | 5     | 13    | 42    |
| Male   | 6     | 16    | 45    |

## End points

### End points reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - low dose level (Steady State - PK study) |
|-----------------------|---|

Reporting group description:

Subjects randomized to low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the Leak point pressure (LPP) results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received low dose of 0.025 mg qd (once daily), body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - medium dose level (Steady State - PK study) |
|-----------------------|--|

Reporting group description:

Subjects randomized to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the LPP results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received medium dose of 0.05 mg qd, body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd with and body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - high dose level (Steady State - PK study) |
|-----------------------|--|

Reporting group description:

Subjects randomized to high dose level (0.004–0.008 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight. In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the LPP, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy. Subjects with body weight of 12.1–25.0 kg received high dose of 0.1 mg qd, body weight of 25.1–50.0 kg received high dose of 0.2 mg qd & body weight of 50.1–100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast. One subject randomised to high dose level was not treated. Although actual number of subjects started is 11, 10 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - low dose level (Group D-Denovo) |
|-----------------------|--|

Reporting group description:

Subjects received low dose level (0.001 – 0.002 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 12.1– 25.0 kg received low dose of 0.025 mg qd, body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.



|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - medium dose level (Group D-Denovo) |
|-----------------------|---|

Reporting group description:

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 9.0–12.0 kg received medium dose of 0.025 mg qd as their starting dose, body weight of 12.1–25.0 kg could have titrated to a medium dose of 0.05 mg qd, body weight of 25.1–50.0 kg could have titrated to a medium dose of 0.1 mg qd and body weight of 50.1–100.0 kg could have titrated to a medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - high dose level (Group D-Denovo) |
|-----------------------|---|

Reporting group description:

Subjects titrated to high dose level (0.004–0.008 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 9.0–12.0 kg received high dose of 0.05 mg qd, body weight of 12.1–25.0 kg received high dose of 0.1 mg qd, body weight of 25.1–50.0 kg received high dose of 0.2 mg qd & body weight of 50.1–100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - low dose level (Group D-527.51 Rollover) |
|-----------------------|---|

Reporting group description:

Subjects received low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D- 527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial (527.66). All subjects were to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that that the higher doses would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received low dose of 0.025 mg qd, body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg qd received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|-----------------------|--|

Reporting group description:

Subjects who were to receive medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial. All subjects were to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that the higher doses would provide some efficacy.

Subjects with body weight of 9.0–12.0 kg received medium dose of 0.025 mg qd, body weight of 12.1–25.0 kg received medium dose of 0.05 mg qd, body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd, body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - high dose level (Group D-527.51 Rollover) |
|-----------------------|--|

Reporting group description:

Subjects titrated to high dose level (0.004–0.008 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial. All subjects had to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that the higher doses would provide some efficacy.

Subjects with body weight of 9.0-12.0 kg received high dose of 0.05 mg, body weight of 12.1-25.0 kg received high dose of 0.1 mg, body weight of 25.1-50.0 kg received high dose of 0.2 mg, body weight of 50.1-100.0 kg received high dose of 0.4 mg by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                            |   |
|----------------------------|---|
| Subject analysis set title | PK Study - Single dose (Treatment period) |
| Subject analysis set type  | Intention-to-treat                        |

Subject analysis set description:

The subject analysis type is infact Pharmacokinetics single dose set (PK-SD).

Subjects received low dose level (0.001 – 0.002 mg/kg) of tamsulosin hydrochloride once daily dependent on a subject's body weight (12.1 – 25.0 kg, 25.1 – 50.0 kg and 50.1 – 100.0 kg), by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

All subjects who were randomized, successfully took and retained the first dose of study medication and provided blood samples for PK after single dose were included in the PK-SD set.

In PK Single dose study, it was planned to obtain the Low dose PK data after single dose from all the 30 patients randomized to Low, Medium and high. However as per the protocol amendment, the PK sampling after first drug administration of low dose level was stopped after inclusion of 11 patients and therefore the PK sample of 11 patients were evaluated for PK single dose.

|                            |  |
|----------------------------|--|
| Subject analysis set title | PK Study - Steady state (Treatment period) |
| Subject analysis set type  | Intention-to-treat                         |

Subject analysis set description:

The subject analysis type is infact pharmacokinetics steady state set (PK-SS).

In PK study - steady state, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the Leak point pressure (LPP) results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

pharmacokinetics steady state set (PK-SS): Includes all subjects who were randomized successfully took study medication for two weeks at their randomized dose level and provided blood samples for PK at their steady state visit were included in the PK-SS set.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | D-Denovo (Treatment Period) |
| Subject analysis set type  | Intention-to-treat          |

Subject analysis set description:

The subject analysis type is in fact Treated set.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Treated set (Treat): Includes all subjects who are dispensed study medication and are documented to have taken at least one dose of treatment.

## Primary: Percentage of LLP responders for Group D-Denovo and Group D-527.51 Rollover

|                 |  |
|-----------------|--|
| End point title | Percentage of LLP responders for Group D-Denovo and Group D-527.51 Rollover <sup>[1]</sup> |
|-----------------|--|

End point description:

Group D-Denovo: Leak point pressure (LPP) Response at (response defined as a subject who achieves an LPP pressure <40 cm H<sub>2</sub>O) end of treatment based on two confirmatory values. Group D-527.51 Rollover: Leak point pressure (LPP) Response at (response defined as a subject who achieves an LPP pressure <40 cm H<sub>2</sub>O) last value of the treatment based on two confirmatory values. The last value on

treatment included any final value prior to discontinuation of treatment, regardless of the length of treatment. Detrusor leak point pressure (LPP) recorded in cm H<sub>2</sub>O which was obtained using a standard urodynamic technique, a cystometrogram. Descriptive statistics were used to assess this endpoint. This Outcome Measure was only prespecified for Group D-Denovo & Group D-527.51 Rollover subjects, so results of these two groups are provided. Full Analysis Set for LPP (FAS-LPP): This subject set includes all subjects in Treated set who received one dose of treatment & had one on treatment LPP measurement.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Group D-Denovo: Week 52.

Group D-527.51 Rollover: Week 1, Week 2, Week 3 and Week 4 prior to dose administration and Week 9 (optional), Week 13 (additional), Week 26 (optional) and Week 52 after drug administration.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test was tested.

| End point values                | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|---------------------------------|--|---|---|--|
| Subject group type              | Reporting group                              | Reporting group                                       | Reporting group                                 | Reporting group  |
| Number of subjects analysed     | 26 <sup>[2]</sup>                            | 53 <sup>[3]</sup>                                     | 14 <sup>[4]</sup>                               | 12 <sup>[5]</sup>  |
| Units: percentage of responders |  |   |   |  |
| number (not applicable)         | 73.1   | 67.9  | 35.7  | 58.3   |

Notes:

[2] - FAS-LPP

[3] - FAS-LPP

[4] - FAS-LPP

[5] - FAS-LPP

| End point values                | tamsulosin - high dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |  |
|---------------------------------|---|--|--|--|
| Subject group type              | Reporting group                               | Reporting group  |  |  |
| Number of subjects analysed     | 30 <sup>[6]</sup>                             | 29 <sup>[7]</sup>                                      |  |  |
| Units: percentage of responders |   |  |  |  |
| number (not applicable)         | 26.7  | 20.7   |  |  |

Notes:

[6] - FAS-LPP

[7] - FAS-LPP

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of LPP responders at each visit over time (classified by last value on treatment) for Group D-527.51 Rollover

|                 |   |
|-----------------|---|
| End point title | Number of LPP responders at each visit over time (classified by last value on treatment) for Group D-527.51 Rollover <sup>[8]</sup> |
|-----------------|---|

End point description:

Number of Leak point pressure (LPP) Responders at each visit (week) over time (classified by last value on treatment).

Due to the early termination of the study, most of the LPP assessments were conducted within Weeks 1-9 of treatment. Summary of LPP response rates provided over time. The subjects are classified according to the treatment they were receiving at the last value on treatment. Therefore, no assumptions can be made regarding what dose they were receiving at a particular time point.

LD: Low dose; MD: Medium dose; HD: High dose. This Outcome Measure was only pre-specified for Group D-527.51 Rollover subjects, so results of this group is provided.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 1 (Visit 3) , Week 2 (Visit 4) , Week 3 (Visit 5) and Week 4 (Visit 6) prior to dose administration and Week 9 (Visit 7) (optional), Week 13 (Visit 8) (additional), Week 26 (Visit 9) (optional) and Week 52 (Visit 11) after drug administration.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test was tested.

| End point values                      | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed           | 53 <sup>[9]</sup>                                     | 12 <sup>[10]</sup>                                       | 29 <sup>[11]</sup>                                     |  |
| Units: Participants                   |   |  |  |  |
| number (not applicable)               |   |  |  |  |
| Week 1 (N= 40 (LD), 12 (MD), 27 (HD)) | 38  | 1  | 0  |  |
| Week 2 (N= 2 (LD), 7 (MD), 27 (HD))   | 2   | 7  | 2  |  |
| Week 3 (N= 3 (LD), 0 (MD), 22 (HD))   | 2   | 0  | 5  |  |
| Week 4 (N= 1 (LD), 0 (MD), 3 (HD))    | 1   | 0  | 0  |  |
| Week 9 (N= 7 (LD), 2 (MD), 16 (HD))   | 5   | 2  | 5  |  |
| Week 13 (N= 4 (LD), 0 (MD), 2 (HD))   | 1   | 0  | 1  |  |
| Week 26 (N= 2 (LD), 0 (MD), 3 (HD))   | 1   | 0  | 1  |  |
| Week 52 (N= 1 (LD), 1 (MD), 0 (HD))   | 1   | 1  | 0  |  |

Notes:

[9] - FAS-LPP

[10] - FAS-LPP

[11] - FAS-LPP

## Statistical analyses

No statistical analyses for this end point

## Secondary: Early responders who maintained their LPP below 40 cm H2O during the study for Group D-Denovo and Group D-527.51 Rollover

|                 |   |
|-----------------|---|
| End point title | Early responders who maintained their LPP below 40 cm H2O during the study for Group D-Denovo and Group D-527.51 Rollover |
|-----------------|---|

End point description:

Early responders who maintained their detrusor LPP below 40 cm H2O during the study.

Timeframe for Group D-Denovo: Low dose: Week (wk) 1, 3 & 4 prior to dose and Week 2, 9 & 26 (optional), 13(additional) & 52 post dose. Medium dose: Week 1, 2 & 4 prior to dose and Week 3, 9(optional), 13(additional), 26 (optional) & 52 post dose. High dose: Week 1, 2 & 3 prior to dose administration and Week 4, 9(optional), 13(additional), 26 (optional) & 52 post dose. Group D-527.51 Rollover: Week 1, 2, 3 & 4 prior to dose and Week 9 & 26 (optional), 13 (additional) & 52 post dose. This Outcome Measure was only pre-specified for Group D-Denovo and Group D-527.51 Rollover subjects, However this endpoint was analysed for the Group D-Denovo and it was not analysed for Group D-

527.51 Rollover as very limited data were collected due to the early termination of the study and no alternative endpoint was also defined in the Group D-527.51 rollover, so only the results for Group D-Denovo is provided.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Week 1 to Week 52 (Time frame for all weeks are described study wise in the Description). |           |

| End point values            | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|-----------------------------|--|---|---|--|
| Subject group type          | Reporting group                              | Reporting group                                       | Reporting group                                 | Reporting group  |
| Number of subjects analysed | 28 <sup>[12]</sup>                           | 0 <sup>[13]</sup>                                     | 21 <sup>[14]</sup>                              | 0 <sup>[15]</sup>  |
| Units: Participants         |  |   |   |  |
| number (not applicable)     | 17   |   | 5   |  |

Notes:

[12] - FAS-LPP

[13] - This endpoint was not analysed due to insufficient data so no results have been analysed.

[14] - FAS-LPP

[15] - This endpoint was not analysed due to insufficient data so no results have been analysed.

| End point values            | tamsulosin - high dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                               | Reporting group  |  |  |
| Number of subjects analysed | 37 <sup>[16]</sup>                            | 0 <sup>[17]</sup>                                      |  |  |
| Units: Participants         |   |  |  |  |
| number (not applicable)     | 3   |  |  |  |

Notes:

[16] - FAS-LPP

[17] - This endpoint was not analysed due to insufficient data so no results have been analysed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in LPP for Group D-527.51 Rollover

|                 |   |
|-----------------|---|
| End point title | Change from baseline in LPP for Group D-527.51 Rollover |
|-----------------|---|

End point description:

Median change from baseline in detrusor leak point pressure (LPP) by treatment group (subjects are classified according to the treatment they were taking at end of treatment (EOT)) and week.

Baseline assessments were obtained from trial 527.51 for Group D-527.51 Rollover. The results from Week 1 were reported because there were very few subjects who reported data at subsequent visits due to the termination of the trial. This Outcome Measure (OM) was only pre-specified for Group D-527.51 Rollover subjects, so results of this group is provided.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline and week 1  |           |

| End point values                              | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |
|---|---|--|--|--|
| Subject group type                            | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                   | 53 <sup>[18]</sup>                                    | 12 <sup>[19]</sup>                                       | 29 <sup>[20]</sup>                                     |  |
| Units: cm H2O                                 |   |  |  |  |
| median (standard deviation)                   |   |  |  |  |
| Baseline (N= 53 (LD), 12 (MD), 29 (HD))       | 48.5 (± 14.47)  | 48.5 (± 11.19)   | 55.5 (± 24.52)   |  |
| Week 1 - Actual (N= 39 (LD), 9 (MD), 22 (HD)) | 29 (± 8.5)  | 49.5 (± 8.3)   | 64.75 (± 27.2)   |  |
| Week 1 - Change (N= 39 (LD), 9 (MD), 22 (HD)) | -25.5 (± 15.18)                                       | -2 (± 13.68)   | -1.25 (± 24.97)  |  |

Notes:

[18] - FAS-LPP

[19] - FAS-LPP

[20] - FAS-LPP

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent change from baseline in LPP for Group D-527.51 Rollover

|                 |   |
|-----------------|---|
| End point title | Percent change from baseline in LPP for Group D-527.51 Rollover |
|-----------------|---|

End point description:

Percent change from baseline in actual detrusor leak point pressure (LPP) by treatment group (subjects are classified according to the treatment they were taking at end of treatment) and Week.

Baseline assessments were obtained from trial 527.51 for Group D-527.51 Rollover. The results from Week 1 were reported because there were very few subjects who reported data at subsequent visits due to the termination of the trial. This Outcome Measure was only pre-specified for Group D-527.51 Rollover subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 1

| End point values                        | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |
|---|---|--|--|--|
| Subject group type                      | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed             | 53 <sup>[21]</sup>                                    | 12 <sup>[22]</sup>                                       | 29 <sup>[23]</sup>                                     |  |
| Units: percent change                   |   |  |  |  |
| median (standard deviation)             |   |  |  |  |
| Baseline (N= 53 (LD), 12 (MD), 29 (HD)) | 48.5 (± 14.47)  | 48.5 (± 11.19)   | 55.5 (± 24.52)   |  |

|   |                       |                      |                      |  |
|---|-----------------------|----------------------|----------------------|--|
| Week 1 - Actual (N= 39 (LD), 9 (MD), 22 (HD)) | 29 ( $\pm$ 8.5)       | 49.5 ( $\pm$ 8.3)    | 64.75 ( $\pm$ 27.2)  |  |
| Week 1 - Change (N= 39 (LD), 9 (MD), 22 (HD)) | -48.48 ( $\pm$ 18.65) | -3.88 ( $\pm$ 22.43) | -2.71 ( $\pm$ 40.41) |  |

Notes:

[21] - FAS-LPP

[22] - FAS-LPP

[23] - FAS-LPP

## Statistical analyses

No statistical analyses for this end point

## Secondary: Response defined as stabilization or improvement of hydroureter measured by renal ultrasound compared to baseline for Group D-Denovo and Group D-527.51 Rollover

|                 |  |
|-----------------|--|
| End point title | Response defined as stabilization or improvement of hydroureter measured by renal ultrasound compared to baseline for Group D-Denovo and Group D-527.51 Rollover |
|-----------------|--|

End point description:

Response defined as stabilization or improvement of hydroureter measured by renal ultrasound compared to baseline by treatment group (subjects classified according to treatment they were taking at wk 52 or EOT) at wk 52 for Group D-Denovo & (subjects classified according to treatment they were taking at EOT) at LVOT for Group D-527.51 Rollover. Baseline assessments were obtained from trial 527.51 for Group D-527.51 Rollover. The overall treatment duration was not sufficient to reach any meaningful conclusions regarding improvement or stabilization of hydroureter in Group D-527.51 Rollover. Hydroureter response is defined as improvement or stabilization based upon the presence or absence of hydroureter at EOT compared to baseline. This OM was only pre-specified for Group D-Denovo & Group D-527.51 Rollover subjects, so results of these two groups are provided. FAS for Renal (FAS-RENAL): Includes all patients in the Treated set who received one dose of treatment and had one treatment renal measurement.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group D-Denovo: Baseline and Week 52

Group D-527.51 Rollover: Baseline, Week 26 and Week 52.

| End point values            | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|-----------------------------|--|---|---|--|
| Subject group type          | Reporting group                              | Reporting group                                       | Reporting group                                 | Reporting group  |
| Number of subjects analysed | 27 <sup>[24]</sup>                           | 44 <sup>[25]</sup>                                    | 17 <sup>[26]</sup>                              | 8 <sup>[27]</sup>  |
| Units: Participants         |  |   |   |  |
| Right Kidney                | 26   | 43  | 15  | 8  |
| Left Kidney                 | 24   | 43  | 14  | 8  |

Notes:

[24] - FAS-RENAL

[25] - FAS-RENAL

[26] - FAS-RENAL

[27] - FAS-RENAL

|                  |  |  |  |  |
|------------------|--|--|--|--|
| End point values | tamsulosin - high dose level (Group D- | tamsulosin - high dose level (Group D- |  |  |
|------------------|--|--|--|--|

|                             | Denovo)            | 527.51 Rollover)   |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 34 <sup>[28]</sup> | 19 <sup>[29]</sup> |  |  |
| Units: Participants         |                    |                    |  |  |
| Right Kidney                | 28                 | 19                 |  |  |
| Left Kidney                 | 29                 | 17                 |  |  |

Notes:

[28] - FAS-RENAL

[29] - FAS-RENAL

## Statistical analyses

No statistical analyses for this end point

### Secondary: Response defined as stabilization or improvement of hydronephrosis measured by renal ultrasound compared to baseline for Group D-Denovo and Group D-527.51 Rollover

|                 |   |
|-----------------|---|
| End point title | Response defined as stabilization or improvement of hydronephrosis measured by renal ultrasound compared to baseline for Group D-Denovo and Group D-527.51 Rollover |
|-----------------|---|

End point description:

Response defined as stabilization or improvement of hydronephrosis measured by renal ultrasound compared to baseline by treatment group (subjects are classified according to the treatment they were taking at wk 52 or EOT) at wk 52 for Group D-Denovo & (subjects classified according to the treatment they were taking at EOT) at last value on treatment (LVOT) for Group D-527.51 Rollover. Baseline assessments were obtained from trial 527.51 for Group D-527.51 Rollover. Overall treatment duration was not sufficient to reach any meaningful conclusions regarding improvement or stabilization of hydronephrosis in the Group D-527.51 rollover. Hydronephrosis response is defined as improvement or stabilization based upon ultrasound grading at the end of the study. The lower or same grade at EOT compared to baseline is considered an improvement or stabilization. This Outcome Measure was only pre-specified for Group D-Denovo and Group D-527.51 Rollover subjects, so results of these two groups are provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group D-Denovo: Baseline and Week 52.

Group D-527.51 Rollover: Baseline, Week 26 and Week 52.

| End point values            | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|-----------------------------|--|---|---|--|
| Subject group type          | Reporting group                              | Reporting group                                       | Reporting group                                 | Reporting group  |
| Number of subjects analysed | 27 <sup>[30]</sup>                           | 44 <sup>[31]</sup>                                    | 17 <sup>[32]</sup>                              | 8 <sup>[33]</sup>  |
| Units: Participants         |  |   |   |  |
| Right Kidney                | 26   | 39  | 15  | 8  |
| Left Kidney                 | 24   | 42  | 14  | 7  |

Notes:

[30] - Full analysis set (FAS-RENAL)

[31] - Full analysis set (FAS-RENAL)

[32] - Full analysis set (FAS-RENAL)

[33] - Full analysis set (FAS-RENAL)



| End point values            | tamsulosin - high dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                               | Reporting group  |  |  |
| Number of subjects analysed | 34 <sup>[34]</sup>                            | 19 <sup>[35]</sup>                                     |  |  |
| Units: Participants         |   |  |  |  |
| Right Kidney                | 28  | 17   |  |  |
| Left Kidney                 | 26  | 17   |  |  |

Notes:

[34] - Full analysis set (FAS-RENAL)

[35] - Full analysis set (FAS-RENAL)

## Statistical analyses

No statistical analyses for this end point

## Secondary: LPP response at any time during the trial for Group D-Denovo and Group D-527.51 Rollover

|                 |  |
|-----------------|--|
| End point title | LPP response at any time during the trial for Group D-Denovo and Group D-527.51 Rollover |
|-----------------|--|

End point description:

Response rates of LPP responders (2 LPP values < 40 cm H2O) at any time during the trial by treatment group.

Timeframe for Group D-Denovo: Low dose: Week 1, 3 & 4 prior to dose and Week 2, 9 & 26 (optional), 13(additional) & 52 post dose. Medium dose: Week 1, 2 & 4 prior to dose and Week 3, 9(optional), 13(additional), 26 (optional) & 52 post dose. High dose: Week 1, 2 & 3 prior to dose administration and Week 4, 9(optional), 13(additional), 26 (optional) & 52 post dose. Group D-527.51 Rollover: Week 1, 2, 3 & 4 prior to dose and Week 9 & 26 (optional), 13 (additional) & 52 post dose. This Outcome Measure was only pre-specified for Group D-Denovo and Group D-527.51 Rollover subjects, so results of these two groups are provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 1 to Week 52 (described study wise in the Description).

| End point values            | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|-----------------------------|--|---|---|--|
| Subject group type          | Reporting group                              | Reporting group                                       | Reporting group                                 | Reporting group  |
| Number of subjects analysed | 28 <sup>[36]</sup>                           | 53 <sup>[37]</sup>                                    | 21 <sup>[38]</sup>                              | 12 <sup>[39]</sup>                                       |
| Units: participants         | 26   | 42  | 16  | 8  |

Notes:

[36] - FAS-LPP

[37] - FAS-LPP

[38] - FAS-LPP

[39] - FAS-LPP

| End point values | tamsulosin - high dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-527.51) |  |  |
|------------------|---|---|--|--|
|------------------|---|---|--|--|

|                             |                    | Rollover)          |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 37 <sup>[40]</sup> | 29 <sup>[41]</sup> |  |  |
| Units: participants         | 16                 | 12                 |  |  |

Notes:

[40] - FAS-LPP

[41] - FAS-LPP

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with Clinically Relevant Abnormalities for Physical Examination, Vital Signs/Orthostatic testing, Electorocardiogram (ECG),Laboratory Values,Urinalysis,Occurence of Adverse events & Cognitive Testing for Group D-527.51 Rollover

|                 |  |
|-----------------|--|
| End point title | Number of participants with Clinically Relevant Abnormalities for Physical Examination, Vital Signs/Orthostatic testing, Electorocardiogram (ECG),Laboratory Values,Urinalysis,Occurence of Adverse events & Cognitive Testing for Group D-527.51 Rollover |
|-----------------|--|

End point description:

Number of participants with Clinically Relevant Abnormalities for Physical Examination, Vital Signs/Orthostatic testing, Electrocardiogram (ECG), Laboratory Values, Urinalysis, Occurence of Adverse events and Cognitive Testing.

Relevant findings or worsening of baseline conditions were reported as adverse events.Below mentioned result are the number of subjects who had the clinical relevant abnormalities for the preferred term 'Hepatic enzyme increased'. This Outcome Measure was only prespecified for Group D-527.51 Rollover subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first drug administration until 28 days after last study drug administration, upto 395 days

| End point values            | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed | 54 <sup>[42]</sup>                                    | 13 <sup>[43]</sup>                                       | 29 <sup>[44]</sup>                                     |  |
| Units: Participants         |   |  |  |  |
| Hepatic enzyme increased    | 1   | 0  | 0  |  |

Notes:

[42] - Treated Set (TS)

[43] - Treated Set (TS)

[44] - Treated Set (TS)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with Clinically Relevant Abnormalities for Physical Examination, Vital Signs/Orthostatic testing, Electorocardiogram (ECG),

## Laboratory Values, Urinalysis, Occurrence of Adverse events and Cognitive Testing for Group D-Denovo

|                 |  |
|-----------------|--|
| End point title | Number of participants with Clinically Relevant Abnormalities for Physical Examination, Vital Signs/Orthostatic testing, ECG, Laboratory Values, Urinalysis, Occurrence of Adverse events and Cognitive Testing for Group D-Denovo |
|-----------------|--|

### End point description:

Number of participants with Clinically Relevant Abnormalities for Physical Examination, Vital Signs/Orthostatic testing, Electrocardiogram (ECG), Laboratory Values, Urinalysis, Occurrence of Adverse events and Cognitive Testing.

Relevant findings or worsening of baseline conditions were reported as adverse events.

Subjects who experienced orthostatic hypotension during orthostatic testing were reported as adverse events. This Outcome Measure was only pre-specified for Group D-Denovo, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

### End point timeframe:

From first drug administration until 28 days after last study drug administration, upto 450 days

| End point values            | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-Denovo) |  |
|-----------------------------|--|---|---|--|
| Subject group type          | Reporting group                              | Reporting group                                 | Reporting group                               |  |
| Number of subjects analysed | 29 <sup>[45]</sup>                           | 21 <sup>[46]</sup>                              | 37 <sup>[47]</sup>                            |  |
| Units: Participants         |  |   |   |  |
| Blood urine present         | 0  | 0   | 1   |  |
| Body temperature increased  | 0  | 0   | 1   |  |
| Orthostatic hypotension     | 1  | 3   | 0   |  |

### Notes:

[45] - Treated Set (TS)

[46] - Treated Set (TS)

[47] - Treated Set (TS)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vision Testing for Group D-527.51 Rollover

|                 |  |
|-----------------|--|
| End point title | Vision Testing for Group D-527.51 Rollover |
|-----------------|--|

### End point description:

Number of subjects with a change from baseline in visual acuity by treatment group (subjects are classified according to the treatment they were taking at end of treatment).

They were analysed based on the below mentioned category in both the Eyes:

- 1) No Change
- 2) Decrease in visual acuity
- 3) Increase in visual acuity
- 4) Missing

Missing includes subjects with no baseline exam and subjects with exam scores missing. This Outcome Measure was only pre-specified for Group D-527.51 Rollover subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26 and Week 52

| End point values                      | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed           | 54 <sup>[48]</sup>                                    | 13 <sup>[49]</sup>                                       | 29 <sup>[50]</sup>                                     |  |
| Units: Participants                   |   |  |  |  |
| Right Eye - No Change                 | 32  | 10   | 12   |  |
| Right Eye - Decrease in visual acuity | 5   | 2  | 4  |  |
| Right Eye - Increase in visual acuity | 12  | 1  | 6  |  |
| Right Eye - Missing                   | 5   | 0  | 7  |  |
| Left Eye - No Change                  | 31  | 12   | 12   |  |
| Left Eye - Decrease in visual acuity  | 8   | 1  | 3  |  |
| Left Eye - Increase in visual acuity  | 10  | 0  | 7  |  |
| Left Eye - Missing                    | 5   | 0  | 7  |  |

Notes:

[48] - Treated Set (TS)

[49] - Treated Set (TS)

[50] - Treated Set (TS)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vision Testing for Group D-Denovo

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Vision Testing for Group D-Denovo |
|-----------------|-----------------------------------|

End point description:

Number of subjects with a change from baseline in visual acuity by treatment group (subjects are classified according to the treatment they were taking at Week 52 or end of treatment).

They were analysed based on the below mentioned category in both the Eyes:

- 1) No Change
- 2) Decrease in visual acuity
- 3) Increase in visual acuity
- 4) Missing

Missing includes subjects with no baseline exam and subjects with exam scores missing. This Outcome Measure was only pre-specified for Group D-Denovo subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 26 and Week 52.

| End point values                                | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-Denovo) |  |
|---|--|---|---|--|
| Subject group type                              | Reporting group                              | Reporting group                                 | Reporting group                               |  |
| Number of subjects analysed                     | 29 <sup>[51]</sup>                           | 21 <sup>[52]</sup>                              | 37 <sup>[53]</sup>                            |  |
| Units: Participants                             |  |   |   |  |
| Right Eye (Week 26) - No Change                 | 11   | 7   | 12  |  |
| Right Eye (Week 26) - Decrease in visual acuity | 8  | 1   | 8   |  |
| Right Eye (Week 26) - Increase in visual acuity | 8  | 4   | 11  |  |
| Right Eye (Week 26) - Missing                   | 2  | 9   | 6   |  |
| Left Eye (Week 26) - No Change                  | 11   | 6   | 19  |  |
| Left Eye (Week 26) - Decrease in visual acuity  | 7  | 1   | 4   |  |
| Left Eye (Week 26) - Increase in visual acuity  | 9  | 5   | 8   |  |
| Left Eye (Week 26) - Missing                    | 2  | 9   | 6   |  |
| Right Eye (Week 52) - No Change                 | 7  | 6   | 16  |  |
| Right Eye (Week 52) - Decrease in visual acuity | 10   | 2   | 4   |  |
| Right Eye (Week 52) - Increase in visual acuity | 11   | 6   | 12  |  |
| Right Eye (Week 52) - Missing                   | 1  | 7   | 5   |  |
| Left Eye (Week 52) - No Change                  | 11   | 5   | 12  |  |
| Left Eye (Week 52) - Decrease in visual acuity  | 6  | 3   | 6   |  |
| Left Eye (Week 52) - Increase in visual acuity  | 11   | 7   | 14  |  |
| Left Eye (Week 52) - Missing                    | 1  | 6   | 5   |  |

Notes:

[51] - Treated Set (TS)

[52] - Treated Set (TS)

[53] - Treated Set (TS)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax,1

|                 |        |
|-----------------|--------|
| End point title | Cmax,1 |
|-----------------|--------|

End point description:

Maximum measured concentration of the analyte in plasma following the first dose, Cmax,1.

Pharmacokinetics single dose set (PK-SD): This set includes subjects who were randomized, successfully took and retained the first dose of study medication and provided blood samples for PK at Visit 2.

This Outcome Measure was only pre-specified for PK Study- single dose group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h and 8h after the drug administration.

| End point values                                    | PK Study - Single dose (Treatment period) |  |  |  |
|---|---|--|--|--|
| Subject group type                                  | Subject analysis set                      |  |  |  |
| Number of subjects analysed                         | 11 <sup>[54]</sup>                        |  |  |  |
| Units: ng/mL  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 1.67 (± 68.8)                             |  |  |  |

Notes:

[54] - Pharmacokinetics single dose set (PK-SD)

### Statistical analyses

No statistical analyses for this end point

### Secondary: tmax, 1

|                 |         |
|-----------------|---------|
| End point title | tmax, 1 |
|-----------------|---------|

End point description:

Time from dosing to maximum measured concentration of the analyte in plasma after administration of the first dose, tmax, 1.

This Outcome Measure was only pre-specified for PK Study- single dose group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h and 8h after the drug administration.

| End point values              | PK Study - Single dose (Treatment period) |  |  |  |
|-------------------------------|---|--|--|--|
| Subject group type            | Subject analysis set                      |  |  |  |
| Number of subjects analysed   | 11 <sup>[55]</sup>                        |  |  |  |
| Units: hours                  |   |  |  |  |
| median (full range (min-max)) | 6 (2 to 8)                                |  |  |  |

Notes:

[55] - Pharmacokinetics single dose set (PK-SD)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cmax, 1 ,DW ,norm

|                 |                   |
|-----------------|-------------------|
| End point title | Cmax, 1 ,DW ,norm |
|-----------------|-------------------|

End point description:

Dose- and weight-normalized Cmax,1 (Cmax,1,DW,norm).

Weight normalization of Cmax,1 was performed by dividing the respective quantities by the reciprocal of body weight in kg. This Outcome Measure was only pre-specified for PK Study- single dose group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h and 8h after the drug administration.

| End point values                                    | PK Study - Single dose (Treatment period) |  |  |  |
|---|---|--|--|--|
| Subject group type                                  | Subject analysis set                      |  |  |  |
| Number of subjects analysed                         | 11 <sup>[56]</sup>                        |  |  |  |
| Units: ng/mL/mg*kg                                  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 1120 (± 67.2)                             |  |  |  |

Notes:

[56] - Pharmacokinetics single dose set (PK-SD)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cpre,ss

|                 |         |
|-----------------|---------|
| End point title | Cpre,ss |
|-----------------|---------|

End point description:

Pre-dose concentration of the analyte in plasma at steady state immediately before administration of the next dose, Cpre,ss.

Pharmacokinetics steady state set (PK-SS): This set includes subjects who were randomized successfully took study medication for two weeks at their randomized dose level and provided blood samples for PK at their steady state visit. This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 9 <sup>[57]</sup>                                     | 9 <sup>[58]</sup>  | 10 <sup>[59]</sup>                                     |  |
| Units: ng/mL  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 0.914 (± 159)   | 1.83 (± 131)   | 4.03 (± 70.6)  |  |

Notes:

[57] - pharmacokinetics steady state set (PK-SS)

[58] - Pharmacokinetics steady state set (PK-SS)

[59] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

**Secondary: C<sub>max,ss</sub>**

|  |                     |
|--|---------------------|
| End point title  | C <sub>max,ss</sub> |
| End point description:<br>Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval $\tau$ , C <sub>max,ss</sub> . This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided. |                     |
| End point type   | Secondary           |
| End point timeframe:<br>-0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.   |                     |

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[60]</sup>                                    | 9 <sup>[61]</sup>  | 10 <sup>[62]</sup>                                     |  |
| Units: ng/mL  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 2.79 (± 59.5)   | 5.02 (± 94.8)  | 14.1 (± 50.3)  |  |

Notes:

[60] - Pharmacokinetics steady state set (PK-SS)

[61] - Pharmacokinetics steady state set (PK-SS)

[62] - Pharmacokinetics steady state set (PK-SS)

**Statistical analyses**

|   |   |
|---|---|
| Statistical analysis title  | C <sub>max,ss</sub> (dose proportionality)  |
| Statistical analysis description:<br>Dose proportionality for C <sub>max,ss</sub> was explored. |   |
| Comparison groups   | tamsulosin - low dose level (Steady State - PK study) v<br>tamsulosin - medium dose level (Steady State - PK study) v<br>tamsulosin - high dose level (Steady State - PK study) |
| Number of subjects included in analysis   | 29  |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[63]</sup>   |
| Parameter estimate  | Slope   |
| Point estimate  | 1.0039  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.6499  |
| upper limit   | 1.3579  |
| Variability estimate  | Standard error of the mean  |
| Dispersion value  | 0.1725  |

Notes:

[63] - Dose proportionality for C<sub>max,ss</sub> was explored based on the regression model. Based on the estimate for the slope parameter, a two sided 95% confidence interval for the slope was computed. Perfect dose proportionality would correspond to a slope of 1.

Standard error of the mean is actually standard error of the slope.



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**Secondary: Cmax,ss, DW, norm**

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|                 |                   |
|-----------------|-------------------|
| End point title | Cmax,ss, DW, norm |
|-----------------|-------------------|

End point description:

Dose- and weight-normalized for Cmax,ss, Cmax,ss, DW, norm.

Weight normalization of Cmax,ss was performed by dividing the respective quantities by the reciprocal of body weight in kg. This Outcome Measure was only pre-specified for PK Study steady state group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.

---

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[64]</sup>                                    | 9 <sup>[65]</sup>  | 10 <sup>[66]</sup>                                     |  |
| Units: ng/mL/mg*kg                                  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 2040 (± 74.3)   | 1850 (± 85.7)  | 2240 (± 47.6)  |  |

Notes:

[64] - Pharmacokinetics steady state set (PK-SS)

[65] - Pharmacokinetics steady state set (PK-SS)

[66] - Pharmacokinetics steady state set (PK-SS)

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Cmin,ss**

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|                 |         |
|-----------------|---------|
| End point title | Cmin,ss |
|-----------------|---------|

End point description:

Minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval  $\tau$ , Cmin,ss. This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.

---

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[67]</sup>                                    | 9 <sup>[68]</sup>  | 10 <sup>[69]</sup>                                     |  |
| Units: ng/mL  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 0.747 (± 99.7)  | 1.52 (± 130)   | 4.01 (± 68.5)  |  |

Notes:

[67] - Pharmacokinetics steady state set (PK-SS)

[68] - Pharmacokinetics steady state set (PK-SS)

[69] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

### Secondary: tmax,ss

|   |           |
|---|-----------|
| End point title   | tmax,ss   |
| End point description:  |           |
| Time from last dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval $\tau$ , tmax,ss. This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided. |           |
| End point type  | Secondary |
| End point timeframe:  |           |
| -0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.  |           |

| End point values              | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|-------------------------------|---|--|--|--|
| Subject group type            | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed   | 10 <sup>[70]</sup>                                    | 9 <sup>[71]</sup>  | 10 <sup>[72]</sup>                                     |  |
| Units: hours                  |   |  |  |  |
| median (full range (min-max)) | 5 (2.33 to 8)   | 5.92 (2 to 8)  | 5.01 (2.23 to 8)                                       |  |

Notes:

[70] - Pharmacokinetics steady state set (PK-SS)

[71] - Pharmacokinetics steady state set (PK-SS)

[72] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

### Secondary: AUC $\tau$ ,ss

|   |                |
|---|----------------|
| End point title   | AUC $\tau$ ,ss |
| End point description:  |                |
| Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval $\tau$ , AUC $\tau$ ,ss. This Outcome Measure was only pre-specified for PK Study- steady state group |                |

subjects, so results of this group is provided.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| -0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration. |           |

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[73]</sup>                                    | 9 <sup>[74]</sup>  | 10 <sup>[75]</sup>                                     |  |
| Units: ng*h/mL                                      |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 35.8 (± 75.6)   | 68.2 (± 94.7)  | 175 (± 61)   |  |

Notes:

[73] - Pharmacokinetics steady state set (PK-SS)

[74] - Pharmacokinetics steady state set (PK-SS)

[75] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | AUC <sub>T,ss</sub> (Dose proportionality) |
|----------------------------|--|

Statistical analysis description:

Dose proportionality for AUC<sub>T,ss</sub> was explored.

|   |   |
|---|---|
| Comparison groups                       | tamsulosin - medium dose level (Steady State - PK study) v<br>tamsulosin - high dose level (Steady State - PK study) v<br>tamsulosin - low dose level (Steady State - PK study) |
| Number of subjects included in analysis | 29  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[76]</sup>   |
| Parameter estimate                      | Slope   |
| Point estimate                          | 0.98  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.5934  |
| upper limit                             | 1.3666  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.1884  |

Notes:

[76] - Dose proportionality for AUC<sub>T,ss</sub> was explored based on the regression model. Based on the estimate for the slope parameter, a two sided 95% confidence interval for the slope was computed. Perfect dose proportionality would correspond to a slope of 1.

Standard error of the mean is actually standard error of the slope.

## Secondary: AUC<sub>T,ss</sub>, DW, norm

|                 |                                |
|-----------------|--------------------------------|
| End point title | AUC <sub>T,ss</sub> , DW, norm |
|-----------------|--------------------------------|

End point description:

Dose- and weight-normalized of AUC<sub>T,ss</sub> ( AUC<sub>T,ss</sub>, DW, norm).

Weight normalization of AUC<sub>τ,ss</sub> was performed by dividing the respective quantities by the reciprocal of body weight in kg. This Outcome Measure was only pre-specified for PK Study steady state group subjects, so results of this group is provided.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| -0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration. |           |

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[77]</sup>                                    | 9 <sup>[78]</sup>  | 10 <sup>[79]</sup>                                     |  |
| Units: ng*h/mL/mg*kg                                |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 26100 (± 91.1)  | 25200 (± 82.9)   | 27700 (± 59.1)   |  |

Notes:

[77] - Pharmacokinetics steady state set (PK-SS)

[78] - Pharmacokinetics steady state set (PK-SS)

[79] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

## Secondary: λ<sub>z,ss</sub>

|   |                   |
|---|-------------------|
| End point title   | λ <sub>z,ss</sub> |
| End point description:  |                   |
| Terminal rate constant of the analyte in plasma at steady state, λ <sub>z,ss</sub> . This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided. |                   |
| End point type  | Secondary         |
| End point timeframe:  |                   |
| -0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.  |                   |

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[80]</sup>                                    | 9 <sup>[81]</sup>  | 10 <sup>[82]</sup>                                     |  |
| Units: 1/hours                                      |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 0.0589 (± 48.1)                                       | 0.0671 (± 40.8)  | 0.0496 (± 31.9)  |  |

Notes:

[80] - Pharmacokinetics steady state set (PK-SS)

[81] - Pharmacokinetics steady state set (PK-SS)

[82] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

### Secondary: t1/2,ss

|                 |         |
|-----------------|---------|
| End point title | t1/2,ss |
|-----------------|---------|

End point description:

Terminal half-life of the analyte in plasma at steady state, t1/2,ss. This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[83]</sup>                                    | 9 <sup>[84]</sup>  | 10 <sup>[85]</sup>                                     |  |
| Units: hours  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 11.8 (± 48.1)   | 10.3 (± 40.8)  | 14 (± 31.9)  |  |

Notes:

[83] - Pharmacokinetics steady state set (PK-SS)

[84] - Pharmacokinetics steady state set (PK-SS)

[85] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

### Secondary: MRTpo,ss

|                 |          |
|-----------------|----------|
| End point title | MRTpo,ss |
|-----------------|----------|

End point description:

Mean residence time of the analyte in the body at steady state after oral administration, MRTpo,ss. This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.

| End point values            | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed | 10 <sup>[86]</sup>                                    | 9 <sup>[87]</sup>  | 10 <sup>[88]</sup>                                     |  |
| Units: hours                |   |  |  |  |

|   |               |             |               |  |
|---|---------------|-------------|---------------|--|
| geometric mean (geometric coefficient of variation) | 18.7 (± 50.5) | 17.6 (± 35) | 20.9 (± 23.6) |  |
|---|---------------|-------------|---------------|--|

Notes:

[86] - Pharmacokinetics steady state set (PK-SS)

[87] - Pharmacokinetics steady state set (PK-SS)

[88] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

### Secondary: CL/F,ss,W,norm

|                 |                |
|-----------------|----------------|
| End point title | CL/F,ss,W,norm |
|-----------------|----------------|

End point description:

Weight-normalized CL/F,ss (apparent clearance of the analyte in the plasma at steady state after extravascular multiple dose administration), CL/F,ss,W,norm.

Weight-normalized CL/F,ss was calculated by dividing the respective quantities by body weight in kg. This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[89]</sup>                                    | 9 <sup>[90]</sup>  | 10 <sup>[91]</sup>                                     |  |
| Units: L/h/kg                                       |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 0.0383 (± 91.1)                                       | 0.0397 (± 82.9)  | 0.0361 (± 59.1)  |  |

Notes:

[89] - Pharmacokinetics steady state set (PK-SS)

[90] - Pharmacokinetics steady state set (PK-SS)

[91] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Vz/F,ss,W,norm

|                 |                |
|-----------------|----------------|
| End point title | Vz/F,ss,W,norm |
|-----------------|----------------|

End point description:

Weight-normalized Vz/F,ss (apparent volume of distribution during the terminal phase λ<sub>z</sub> at steady state following extravascular administration), Vz/F,ss,W,norm.

Weight-normalized VzF,ss was calculated by dividing the respective quantities by body weight in kg. This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results of this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h, 8h, 10h, 24h and 33h after the drug administration.

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       | Reporting group  | Reporting group  |  |
| Number of subjects analysed                         | 10 <sup>[92]</sup>                                    | 9 <sup>[93]</sup>  | 10 <sup>[94]</sup>                                     |  |
| Units: L/kg   |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 0.65 (± 83.8)   | 0.591 (± 103)  | 0.729 (± 96)   |  |

Notes:

[92] - Pharmacokinetics steady state set (PK-SS)

[93] - Pharmacokinetics steady state set (PK-SS)

[94] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses

No statistical analyses for this end point

## Secondary: RA,Cmax

|                 |         |
|-----------------|---------|
| End point title | RA,Cmax |
|-----------------|---------|

End point description:

Accumulation ratios of tamsulosin HCl in plasma at steady state after multiple dose administration over a uniform dosing interval  $\tau$ , expressed as ratio of Cmax at steady state and after single dose.

The accumulation ratio RA,Cmax was calculated as :  $C_{max,ss}/C_{max,1}$ . This Outcome Measure was only pre-specified for PK Study- steady state group subjects, so results from this group is provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

–0.25h prior to dose and 2h, 4h, 6h and 8h after the drug administration.

| End point values                                    | tamsulosin - low dose level (Steady State - PK study) |  |  |  |
|---|---|--|--|--|
| Subject group type                                  | Reporting group                                       |  |  |  |
| Number of subjects analysed                         | 4 <sup>[95]</sup>                                     |  |  |  |
| Units: ng/mL  |   |  |  |  |
| geometric mean (geometric coefficient of variation) | 1.58 (± 65.2)   |  |  |  |

Notes:

[95] - Pharmacokinetics steady state set (PK-SS)

## Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 28 days after last study drug administration, upto 80 days (Steady State - PK study), upto 450 days (Group D-Denovo) and upto 395 days (Group D-527.51 Rollover).

Adverse event reporting additional description:

Subjects were titrated to their efficacious dose. Based on LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up to their higher doses which might have provided some efficacy. Therefore some of the subjects were counted more than once for having reported adverse events with different doses of the study.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - low dose level (Steady State - PK study) |
|-----------------------|---|

Reporting group description:

Subjects randomized to low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the Leak point pressure (LPP) results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received low dose of 0.025 mg qd (once daily), body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - medium dose level (Steady State - PK study) |
|-----------------------|--|

Reporting group description:

Subjects randomized to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the LPP results, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received medium dose of 0.05 mg qd, body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd with and body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - high dose level (Steady State - PK study) |
|-----------------------|--|

Reporting group description:

Subjects randomized to high dose level (0.004–0.008 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight. In PK study, all subjects were titrated to their randomized dose level that they needed to receive which was based on their weight. Depending on the results of the LPP, subjects could remain on that dose if it was found to be efficacious or go back to a lower efficacious dose or titrate up in hopes that the higher dose would provide some efficacy. Subjects with body weight of 12.1–25.0 kg received high dose of 0.1 mg qd, body weight of 25.1–50.0 kg received high dose of 0.2 mg qd & body weight of 50.1–100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast. One subject randomised to high dose level was not treated. Although actual number of subjects started is 11, 10 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - low dose level (Group D-Denovo) |
|-----------------------|--|

Reporting group description:

Subjects received low dose level (0.001 – 0.002 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 12.1– 25.0 kg received low dose of 0.025 mg qd, body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - medium dose level (Group D-Denovo) |
|-----------------------|---|

Reporting group description:

Subjects who were titrated to medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 9.0–12.0 kg received medium dose of 0.025 mg qd as their starting dose, body weight of 12.1–25.0 kg could have titrated to a medium dose of 0.05 mg qd, body weight of 25.1–50.0 kg could have titrated to a medium dose of 0.1 mg qd and body weight of 50.1–100.0 kg could have titrated to a medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - high dose level (Group D-Denovo) |
|-----------------------|---|

Reporting group description:

Subjects titrated to high dose level (0.004–0.008 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-Denovo, all subjects started the study at the Low Dose level, with the exception of the children with a body weight between 9 kg 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 subjects remained on their efficacious dose level for the remainder of the study.

Subjects with body weight of 9.0–12.0 kg received high dose of 0.05 mg qd, body weight of 12.1–25.0 kg received high dose of 0.1 mg qd, body weight of 25.1–50.0 kg received high dose of 0.2 mg qd & body weight of 50.1–100.0 kg received high dose of 0.4 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |   |
|-----------------------|---|
| Reporting group title | tamsulosin - low dose level (Group D-527.51 Rollover) |
|-----------------------|---|

Reporting group description:

Subjects received low dose level (0.001–0.002 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D- 527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial (527.66). All subjects were to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that that the higher doses would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received low dose of 0.025 mg qd, body weight of 25.1–50.0 kg received low dose of 0.05 mg qd and body weight of 50.1–100.0 kg received low dose of 0.1 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt, taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - medium dose level (Group D-527.51 Rollover) |
|-----------------------|--|

Reporting group description:

Subjects who were to receive medium dose level (0.002–0.004 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial. All subjects were to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that the higher doses would provide some efficacy.

Subjects with body weight of 12.1–25.0 kg received low dose of 0.05 mg qd, body weight of 25.1–50.0 kg received medium dose of 0.1 mg qd, body weight of 50.1–100.0 kg received medium dose of 0.2 mg qd by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

|                       |  |
|-----------------------|--|
| Reporting group title | tamsulosin - high dose level (Group D-527.51 Rollover) |
|-----------------------|--|

Reporting group description:

Subjects titrated to high dose level (0.004-0.008 mg/kg) of tamsulosin hydrochloride, once daily dependent on a subject's body weight.

In Group D-527.51 Rollover, once subjects exited the double-blind trial they were rolled over into this trial. All subjects had to titrate to their efficacious dose. Doses that were available were based on subject's weight. Depending on the LPP results, subjects could remain on that dose if it was found to be efficacious or titrate up in hopes that the higher doses would provide some efficacy.

Subjects with body weight of 12.1-25.0 kg received high dose of 0.1 mg, body weight of 25.1-50.0 kg received high dose of 0.2 mg, body weight of 50.1-100.0 kg received high dose of 0.4 mg by sprinkling the content of the capsule(s) over teaspoon of apple sauce or yogurt taken 30 minutes after breakfast.

| Serious adverse events                            | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |
|---|---|--|--|
| Total subjects affected by serious adverse events |   |  |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)  | 1 / 10 (10.00%)  | 0 / 10 (0.00%)   |
| number of deaths (all causes)                     | 0   | 0  | 0  |
| number of deaths resulting from adverse events    | 0   | 0  | 0  |
| Injury, poisoning and procedural complications    |   |  |  |
| Ventriculoperitoneal shunt malfunction            |   |  |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)  | 1 / 10 (10.00%)  | 0 / 10 (0.00%)   |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 1  | 0 / 0  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0  | 0 / 0  |
| Congenital, familial and genetic disorders        |   |  |  |
| Tibial torsion                                    |   |  |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)  | 0 / 10 (0.00%)   | 0 / 10 (0.00%)   |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 0  | 0 / 0  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0  | 0 / 0  |
| Nervous system disorders                          |   |  |  |
| Tethered cord syndrome                            |   |  |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)  | 0 / 10 (0.00%)   | 0 / 10 (0.00%)   |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 0  | 0 / 0  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0  | 0 / 0  |
| Hydrocephalus                                     |   |  |  |
| subjects affected / exposed                       | 0 / 10 (0.00%)  | 0 / 10 (0.00%)   | 0 / 10 (0.00%)   |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 0  | 0 / 0  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0  | 0 / 0  |
| Gastrointestinal disorders                        |   |  |  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Peritoneal cyst                                 |                |                |                |
| subjects affected / exposed                     | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Asthma  |                |                |                |
| subjects affected / exposed                     | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dengue fever                                    |                |                |                |
| subjects affected / exposed                     | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 10 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-Denovo) |
|---|--|---|---|
| Total subjects affected by serious adverse events |  |   |   |
| subjects affected / exposed                       | 2 / 82 (2.44%)                               | 3 / 61 (4.92%)                                  | 4 / 41 (9.76%)                                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| number of deaths (all causes)                   | 0              | 0              | 0              |
| number of deaths resulting from adverse events  | 0              | 0              | 0              |
| Injury, poisoning and procedural complications  |                |                |                |
| Ventriculoperitoneal shunt malfunction          |                |                |                |
| subjects affected / exposed                     | 1 / 82 (1.22%) | 1 / 61 (1.64%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Congenital, familial and genetic disorders      |                |                |                |
| Tibial torsion                                  |                |                |                |
| subjects affected / exposed                     | 0 / 82 (0.00%) | 0 / 61 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Tethered cord syndrome                          |                |                |                |
| subjects affected / exposed                     | 0 / 82 (0.00%) | 0 / 61 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hydrocephalus                                   |                |                |                |
| subjects affected / exposed                     | 2 / 82 (2.44%) | 1 / 61 (1.64%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Peritoneal cyst                                 |                |                |                |
| subjects affected / exposed                     | 1 / 82 (1.22%) | 0 / 61 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Asthma  |                |                |                |
| subjects affected / exposed                     | 0 / 82 (0.00%) | 1 / 61 (1.64%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cellulitis                                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 82 (0.00%) | 0 / 61 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dengue fever                                    |                |                |                |
| subjects affected / exposed                     | 0 / 82 (0.00%) | 1 / 61 (1.64%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 82 (0.00%) | 0 / 61 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 82 (0.00%) | 0 / 61 (0.00%) | 2 / 41 (4.88%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 82 (0.00%) | 0 / 61 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |
|---|---|--|--|
| Total subjects affected by serious adverse events |   |  |  |
| subjects affected / exposed                       | 1 / 93 (1.08%)  | 1 / 41 (2.44%)   | 1 / 29 (3.45%)   |
| number of deaths (all causes)                     | 0   | 0  | 0  |
| number of deaths resulting from adverse events    | 0   | 0  | 0  |
| Injury, poisoning and procedural complications    |   |  |  |
| Ventriculoperitoneal shunt malfunction            |   |  |  |
| subjects affected / exposed                       | 0 / 93 (0.00%)  | 0 / 41 (0.00%)   | 0 / 29 (0.00%)   |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 0  | 0 / 0  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0  | 0 / 0  |
| Congenital, familial and genetic disorders        |   |  |  |
| Tibial torsion                                    |   |  |  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Tethered cord syndrome                          |                |                |                |
| subjects affected / exposed                     | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hydrocephalus                                   |                |                |                |
| subjects affected / exposed                     | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Peritoneal cyst                                 |                |                |                |
| subjects affected / exposed                     | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Asthma  |                |                |                |
| subjects affected / exposed                     | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dengue fever                                    |                |                |                |
| subjects affected / exposed                     | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 93 (0.00%) | 1 / 41 (2.44%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 93 (0.00%) | 1 / 41 (2.44%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 1 / 93 (1.08%) | 0 / 41 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | tamsulosin - low dose level (Steady State - PK study) | tamsulosin - medium dose level (Steady State - PK study) | tamsulosin - high dose level (Steady State - PK study) |
|---|---|--|--|
| Total subjects affected by non-serious adverse events |   |  |  |
| subjects affected / exposed                           | 5 / 10 (50.00%)                                       | 5 / 10 (50.00%)  | 3 / 10 (30.00%)  |
| Investigations  |   |  |  |
| Body temperature increased                            |   |  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 10 (0.00%)   | 1 / 10 (10.00%)  |
| occurrences (all)                                     | 0   | 2  | 0  |
| Vascular disorders                                    |   |  |  |
| Orthostatic hypotension                               |   |  |  |
| subjects affected / exposed                           | 1 / 10 (10.00%)                                       | 1 / 10 (10.00%)  | 0 / 10 (0.00%)   |
| occurrences (all)                                     | 1   | 1  | 0  |
| Nervous system disorders                              |   |  |  |
| Headache  |   |  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 1 / 10 (10.00%)  | 0 / 10 (0.00%)   |
| occurrences (all)                                     | 0   | 1  | 0  |
| Dizziness   |   |  |  |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 10 (0.00%)   | 1 / 10 (10.00%)  |
| occurrences (all)                                     | 0   | 0  | 1  |
| General disorders and administration site conditions  |   |  |  |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 10 (20.00%) | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 2               | 0               | 0               |
| Mass  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Catheter related complication                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Suprapubic pain                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                               | 0               | 0               | 1               |
| Abdominal pain upper                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 0 / 10 (0.00%)  | 1 / 10 (10.00%) |
| occurrences (all)                               | 0               | 0               | 1               |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 10 (10.00%) | 1 / 10 (10.00%) | 1 / 10 (10.00%) |
| occurrences (all)                               | 1               | 1               | 1               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Cough   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Oropharyngeal pain                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Respiratory tract congestion                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 10 (0.00%)  | 1 / 10 (10.00%) | 0 / 10 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 0 / 10 (0.00%)<br>0  | 2 / 10 (20.00%)<br>3 | 0 / 10 (0.00%)<br>0  |
| Renal and urinary disorders<br>Hydronephrosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Psychiatric disorders<br>Nervousness<br>subjects affected / exposed<br>occurrences (all)          | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Infections and infestations<br>Cervicitis<br>subjects affected / exposed<br>occurrences (all)     | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  | 0 / 10 (0.00%)<br>0  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)             | 0 / 10 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 | 0 / 10 (0.00%)<br>0  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 10 (20.00%)<br>2 | 1 / 10 (10.00%)<br>1 | 1 / 10 (10.00%)<br>1 |

| <b>Non-serious adverse events</b>  | tamsulosin - low dose level (Group D-Denovo) | tamsulosin - medium dose level (Group D-Denovo) | tamsulosin - high dose level (Group D-Denovo) |
|--|--|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 51 / 82 (62.20%)                             | 25 / 61 (40.98%)                                | 33 / 41 (80.49%)                              |
| Investigations<br>Body temperature increased   |  |   |   |

|  |   |  |   |
|--|---|--|---|
| subjects affected / exposed<br>occurrences (all)   | 0 / 82 (0.00%)<br>0   | 0 / 61 (0.00%)<br>0  | 1 / 41 (2.44%)<br>1   |
| Vascular disorders<br>Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)  | 1 / 82 (1.22%)<br>1   | 2 / 61 (3.28%)<br>2  | 1 / 41 (2.44%)<br>1   |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 8 / 82 (9.76%)<br>9<br><br>3 / 82 (3.66%)<br>3  | 2 / 61 (3.28%)<br>4<br><br>1 / 61 (1.64%)<br>1   | 3 / 41 (7.32%)<br>3<br><br>1 / 41 (2.44%)<br>1  |
| General disorders and administration<br>site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Mass<br>subjects affected / exposed<br>occurrences (all)<br><br>Catheter related complication<br>subjects affected / exposed<br>occurrences (all)<br><br>Suprapubic pain<br>subjects affected / exposed<br>occurrences (all) | 12 / 82 (14.63%)<br>18<br><br>1 / 82 (1.22%)<br>1<br><br>0 / 82 (0.00%)<br>0<br><br>0 / 82 (0.00%)<br>0 | 3 / 61 (4.92%)<br>4<br><br>0 / 61 (0.00%)<br>0<br><br>0 / 61 (0.00%)<br>0<br><br>0 / 61 (0.00%)<br>0 | 6 / 41 (14.63%)<br>6<br><br>0 / 41 (0.00%)<br>0<br><br>0 / 41 (0.00%)<br>0<br><br>0 / 41 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 4 / 82 (4.88%)<br>4<br><br>3 / 82 (3.66%)<br>3<br><br>4 / 82 (4.88%)<br>5                               | 0 / 61 (0.00%)<br>0<br><br>1 / 61 (1.64%)<br>1<br><br>2 / 61 (3.28%)<br>2                            | 1 / 41 (2.44%)<br>1<br><br>1 / 41 (2.44%)<br>1<br><br>2 / 41 (4.88%)<br>2                             |

|  |                      |                      |                     |
|--|----------------------|----------------------|---------------------|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 9 / 82 (10.98%)<br>9 | 4 / 61 (6.56%)<br>10 | 3 / 41 (7.32%)<br>4 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 7 / 82 (8.54%)<br>8  | 1 / 61 (1.64%)<br>1  | 3 / 41 (7.32%)<br>4 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                       | 3 / 82 (3.66%)<br>3  | 0 / 61 (0.00%)<br>0  | 1 / 41 (2.44%)<br>1 |
| Respiratory tract congestion<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 82 (1.22%)<br>1  | 0 / 61 (0.00%)<br>0  | 0 / 41 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)           | 1 / 82 (1.22%)<br>1  | 2 / 61 (3.28%)<br>2  | 0 / 41 (0.00%)<br>0 |
| Renal and urinary disorders<br>Hydronephrosis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 82 (2.44%)<br>2  | 1 / 61 (1.64%)<br>1  | 3 / 41 (7.32%)<br>3 |
| Psychiatric disorders<br>Nervousness<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 82 (0.00%)<br>0  | 1 / 61 (1.64%)<br>1  | 0 / 41 (0.00%)<br>0 |
| Infections and infestations<br>Cervicitis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 82 (1.22%)<br>1  | 0 / 61 (0.00%)<br>0  | 3 / 41 (7.32%)<br>4 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 4 / 82 (4.88%)<br>4  | 3 / 61 (4.92%)<br>3  | 1 / 41 (2.44%)<br>1 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)  | 3 / 82 (3.66%)<br>4  | 1 / 61 (1.64%)<br>1  | 1 / 41 (2.44%)<br>1 |
| Pharyngitis  |                      |                      |                     |

|                                   |                  |                  |                  |
|-----------------------------------|------------------|------------------|------------------|
| subjects affected / exposed       | 11 / 82 (13.41%) | 1 / 61 (1.64%)   | 2 / 41 (4.88%)   |
| occurrences (all)                 | 12               | 1                | 2                |
| Upper respiratory tract infection |                  |                  |                  |
| subjects affected / exposed       | 1 / 82 (1.22%)   | 1 / 61 (1.64%)   | 3 / 41 (7.32%)   |
| occurrences (all)                 | 1                | 1                | 4                |
| Urinary tract infection           |                  |                  |                  |
| subjects affected / exposed       | 15 / 82 (18.29%) | 11 / 61 (18.03%) | 16 / 41 (39.02%) |
| occurrences (all)                 | 18               | 16               | 23               |

| <b>Non-serious adverse events</b>                     | tamsulosin - low dose level (Group D-527.51 Rollover) | tamsulosin - medium dose level (Group D-527.51 Rollover) | tamsulosin - high dose level (Group D-527.51 Rollover) |
|---|---|--|--|
| Total subjects affected by non-serious adverse events |   |  |  |
| subjects affected / exposed                           | 31 / 93 (33.33%)                                      | 10 / 41 (24.39%)   | 9 / 29 (31.03%)  |
| Investigations  |   |  |  |
| Body temperature increased                            |   |  |  |
| subjects affected / exposed                           | 0 / 93 (0.00%)  | 0 / 41 (0.00%)   | 0 / 29 (0.00%)   |
| occurrences (all)                                     | 0   | 0  | 0  |
| Vascular disorders                                    |   |  |  |
| Orthostatic hypotension                               |   |  |  |
| subjects affected / exposed                           | 0 / 93 (0.00%)  | 0 / 41 (0.00%)   | 0 / 29 (0.00%)   |
| occurrences (all)                                     | 0   | 0  | 0  |
| Nervous system disorders                              |   |  |  |
| Headache  |   |  |  |
| subjects affected / exposed                           | 2 / 93 (2.15%)  | 1 / 41 (2.44%)   | 2 / 29 (6.90%)   |
| occurrences (all)                                     | 2   | 1  | 2  |
| Dizziness   |   |  |  |
| subjects affected / exposed                           | 1 / 93 (1.08%)  | 0 / 41 (0.00%)   | 0 / 29 (0.00%)   |
| occurrences (all)                                     | 1   | 0  | 0  |
| General disorders and administration site conditions  |   |  |  |
| Pyrexia   |   |  |  |
| subjects affected / exposed                           | 1 / 93 (1.08%)  | 1 / 41 (2.44%)   | 1 / 29 (3.45%)   |
| occurrences (all)                                     | 1   | 1  | 1  |
| Mass  |   |  |  |
| subjects affected / exposed                           | 0 / 93 (0.00%)  | 0 / 41 (0.00%)   | 0 / 29 (0.00%)   |
| occurrences (all)                                     | 0   | 0  | 0  |
| Catheter related complication                         |   |  |  |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                 | 0 / 93 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Suprapubic pain<br>subjects affected / exposed<br>occurrences (all)              | 0 / 93 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Gastrointestinal disorders   |                     |                     |                     |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)               | 2 / 93 (2.15%)<br>2 | 0 / 41 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)         | 2 / 93 (2.15%)<br>2 | 0 / 41 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 93 (1.08%)<br>2 | 2 / 41 (4.88%)<br>2 | 0 / 29 (0.00%)<br>0 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 93 (3.23%)<br>4 | 2 / 41 (4.88%)<br>2 | 0 / 29 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders                                  |                     |                     |                     |
| Cough<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 93 (1.08%)<br>1 | 0 / 41 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)           | 1 / 93 (1.08%)<br>1 | 0 / 41 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Respiratory tract congestion<br>subjects affected / exposed<br>occurrences (all) | 0 / 93 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders   |                     |                     |                     |
| Rash<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 93 (0.00%)<br>0 | 1 / 41 (2.44%)<br>1 | 0 / 29 (0.00%)<br>0 |
| Renal and urinary disorders  |                     |                     |                     |
| Hydronephrosis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 93 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0 |

|                                   |                |                |                 |
|-----------------------------------|----------------|----------------|-----------------|
| Psychiatric disorders             |                |                |                 |
| Nervousness                       |                |                |                 |
| subjects affected / exposed       | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%)  |
| occurrences (all)                 | 0              | 0              | 0               |
| Infections and infestations       |                |                |                 |
| Cervicitis                        |                |                |                 |
| subjects affected / exposed       | 0 / 93 (0.00%) | 0 / 41 (0.00%) | 0 / 29 (0.00%)  |
| occurrences (all)                 | 0              | 0              | 0               |
| Nasopharyngitis                   |                |                |                 |
| subjects affected / exposed       | 5 / 93 (5.38%) | 1 / 41 (2.44%) | 2 / 29 (6.90%)  |
| occurrences (all)                 | 6              | 1              | 3               |
| Influenza                         |                |                |                 |
| subjects affected / exposed       | 5 / 93 (5.38%) | 0 / 41 (0.00%) | 0 / 29 (0.00%)  |
| occurrences (all)                 | 6              | 0              | 0               |
| Pharyngitis                       |                |                |                 |
| subjects affected / exposed       | 2 / 93 (2.15%) | 1 / 41 (2.44%) | 1 / 29 (3.45%)  |
| occurrences (all)                 | 2              | 1              | 1               |
| Upper respiratory tract infection |                |                |                 |
| subjects affected / exposed       | 1 / 93 (1.08%) | 1 / 41 (2.44%) | 0 / 29 (0.00%)  |
| occurrences (all)                 | 1              | 1              | 0               |
| Urinary tract infection           |                |                |                 |
| subjects affected / exposed       | 9 / 93 (9.68%) | 3 / 41 (7.32%) | 4 / 29 (13.79%) |
| occurrences (all)                 | 16             | 6              | 4               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 23 January 2006 | 1) Inclusion criteria changed to include patients up to 16 years of age (previously 15 years of age maximum)<br>2) Terminology "end of study" was used incorrectly and changed to "end of treatment" where applicable.<br>3) Additional safety monitoring was implemented, including additional ECG (Visit 9), urinalysis, and recording of post-void residual for specific visits.<br>4) Study population was further described as "patient with elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida)".<br>5) Hormonal assays were added at Visit 9 for Group D-Rollover patients.   |
| 23 October 2006 | 1) After first 11 patients provided first-dose PK samples, first-dose PK sampling was made optional for all future patients<br>2) Due to altered PK sampling on Day 1 (Visit 2), vital sign testing and orthostatic testing were decreased.<br>3) The detrusor leak point pressure eligibility requirements were clarified<br>4) The addition of recent Botox injections used for urological disease management was added as an exclusion criterion.<br>5) Yogurt was added as an alternative drug administration vehicle, the amount of vehicle was specified, and the need to take a spoonful of water after administration of the drug was added.<br>6) The study drug storage conditions were further clarified |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption   | Restart date |
|--------------|--|--------------|
| 30 June 2009 | The Group D-Rollover portion of Study 527.66 was terminated early based on data from placebo-controlled Study 527.51 that showed lack of efficacy in reducing LPP to <40 cm H <sub>2</sub> O. Reductions in detrusor LPP were observed for some patients during the study. | -            |

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In Group D-527.51 Rollover study, due to the early termination caution should be used in interpreting these results due to the impact of the early termination, as well as the impact of the study design on interpretation of results by dose.

Notes: