



## Clinical trial results:

### A Multicentre, Open-label, Single Ascending Dose Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Mirabegron OCAS Tablets in Pediatric Subjects from 5 to Less than 18 Years of Age with Neurogenic Detrusor Overactivity (NDO) or Overactive Bladder (OAB)

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2014-000340-15    |
| Trial protocol           | DE BE NO DK       |
| Global end of trial date | 21 September 2015 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 30 March 2016 |
| First version publication date | 30 March 2016 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 178-CL-202 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02211846 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                              |
|------------------------------|--------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Astellas Pharma Europe B.V.                                                                                  |
| Sponsor organisation address | Sylviusweg 62, Leiden, Netherlands, 2333 BE                                                                  |
| Public contact               | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |
| Scientific contact           | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |

Notes:

#### Paediatric regulatory details

|                                                                      |                                          |
|----------------------------------------------------------------------|------------------------------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                                      |
| EMA paediatric investigation plan number(s)                          | EMA-000597-PIP10-04, EMA-000597-PIP15-01 |
| 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                       | 21 September 2015 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 21 September 2015 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics of mirabegron Oral Controlled Absorption System (OCAS) tablets after single-dose administration at different dose levels in children and adolescents with NDO or OAB.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 21 September 2014 |
| 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 | Belgium: 1  |
| Country: Number of subjects enrolled | Denmark: 11 |
| Country: Number of subjects enrolled | Norway: 8   |
| Country: Number of subjects enrolled | Poland: 14  |
| Worldwide total number of subjects   | 34          |
| EEA total number of subjects         | 34          |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| 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)                     | 19 |

|                           |    |
|---------------------------|----|
| Adolescents (12-17 years) | 15 |
| Adults (18-64 years)      | 0  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Children and adolescents with NDO or OAB, who consented to enter this study and fulfilled all the eligibility criteria were enrolled. A wash-out of prohibited medication for 5 half-lives was performed if a participant was using prohibited medication.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                              |                            |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes                        |
| <b>Arm title</b>             | Adolescents Low Dose (Fed) |

Arm description:

Adolescents aged 12 to less than 18 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 55.0 kg received 25 mg mirabegron; participants  $\geq$  55.0 kg received 50 mg (both referred to as low dose, predicted to achieve the low exposure target).

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Mirabegron           |
| Investigational medicinal product code | YM178                |
| Other name                             | Myrbetriq®, Betmiga™ |
| Pharmaceutical forms                   | Tablet               |
| Routes of administration               | Oral use             |

Dosage and administration details:

Participants received a single dose of mirabegron prolonged-release tablet/s (with strengths of 25 mg or 50 mg), with a glass of water on day 1.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Children Low Dose (Fed) |
|------------------|-------------------------|

Arm description:

Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 55.0 kg received 25 mg mirabegron; participants  $\geq$  55.0 kg received 50 mg (both referred to as low dose, predicted to achieve the low exposure target).

|                                        |                      |
|----------------------------------------|----------------------|
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| Pharmaceutical forms                   | Tablet               |
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Dosage and administration details:

Participants received a single dose of mirabegron prolonged-release tablet/s (with strengths of 25 mg or 50 mg), with a glass of water on day 1.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Adolescents High Dose (Fed) |
|------------------|-----------------------------|

Arm description:

Adolescents aged 12 to less than 18 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants  $\geq$  40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).

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

|                                        |                      |
|----------------------------------------|----------------------|
| Investigational medicinal product name | Mirabegron           |
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|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Children High Dose (Fed) |
|------------------|--------------------------|

Arm description:

Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants ≥ 40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Mirabegron           |
| Investigational medicinal product code | YM178                |
| Other name                             | Myrbetriq®, Betmiga™ |
| Pharmaceutical forms                   | Tablet               |
| Routes of administration               | Oral use             |

Dosage and administration details:

Participants received a single dose of mirabegron prolonged-release tablet/s (with strengths of 25 mg or 50 mg), with a glass of water on day 1.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Children High Dose (Fasted) |
|------------------|-----------------------------|

Arm description:

Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron under fasted conditions (fasted from at least midnight the day before until 4 hours after dosing). Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants ≥ 40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Mirabegron           |
| Investigational medicinal product code | YM178                |
| Other name                             | Myrbetriq®, Betmiga™ |
| Pharmaceutical forms                   | Tablet               |
| Routes of administration               | Oral use             |

Dosage and administration details:

Participants received a single dose of mirabegron prolonged-release tablet/s (with strengths of 25 mg or 50 mg), with a glass of water on day 1.

| <b>Number of subjects in period 1</b> | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) |
|---------------------------------------|----------------------------|-------------------------|-----------------------------|
| Started                               | 7                          | 7                       | 8                           |
| Safety Analysis Set (SAF)             | 7                          | 7                       | 8                           |
| Pharmacokinetic Analysis Set (PKAS)   | 7                          | 7                       | 8                           |
| Completed                             | 7                          | 7                       | 8                           |

| <b>Number of subjects in period 1</b> | Children High Dose (Fed) | Children High Dose (Fasted) |
|---------------------------------------|--------------------------|-----------------------------|
| Started                               | 6                        | 6                           |

|                                     |   |   |
|-------------------------------------|---|---|
| Safety Analysis Set (SAF)           | 6 | 6 |
| Pharmacokinetic Analysis Set (PKAS) | 6 | 6 |
| Completed                           | 6 | 6 |

## Baseline characteristics

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Adolescents Low Dose (Fed) |
|-----------------------|----------------------------|

Reporting group description:

Adolescents aged 12 to less than 18 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 55.0 kg received 25 mg mirabegron; participants  $\geq$  55.0 kg received 50 mg (both referred to as low dose, predicted to achieve the low exposure target).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Children Low Dose (Fed) |
|-----------------------|-------------------------|

Reporting group description:

Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 55.0 kg received 25 mg mirabegron; participants  $\geq$  55.0 kg received 50 mg (both referred to as low dose, predicted to achieve the low exposure target).

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Adolescents High Dose (Fed) |
|-----------------------|-----------------------------|

Reporting group description:

Adolescents aged 12 to less than 18 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants  $\geq$  40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Children High Dose (Fed) |
|-----------------------|--------------------------|

Reporting group description:

Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants  $\geq$  40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Children High Dose (Fasted) |
|-----------------------|-----------------------------|

Reporting group description:

Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron under fasted conditions (fasted from at least midnight the day before until 4 hours after dosing). Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants  $\geq$  40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).

| Reporting group values | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) |
|------------------------|----------------------------|-------------------------|-----------------------------|
| Number of subjects     | 7                          | 7                       | 8                           |
| Age categorical        |                            |                         |                             |
| Units: Subjects        |                            |                         |                             |

|                        |           |           |           |
|------------------------|-----------|-----------|-----------|
| Age continuous         |           |           |           |
| Units: years           |           |           |           |
| arithmetic mean        | 14.9      | 8.1       | 14.1      |
| standard deviation     | $\pm$ 1.6 | $\pm$ 0.9 | $\pm$ 1.6 |
| Gender categorical     |           |           |           |
| Units:                 |           |           |           |
| Male                   | 2         | 2         | 2         |
| Female                 | 5         | 5         | 6         |
| Diagnosis at Screening |           |           |           |
| Units: Subjects        |           |           |           |
| NDO                    | 2         | 2         | 3         |
| OAB                    | 5         | 5         | 5         |

| Reporting group values | Children High Dose (Fed) | Children High Dose (Fasted) | Total |
|------------------------|--------------------------|-----------------------------|-------|
|------------------------|--------------------------|-----------------------------|-------|

|                                                                         |              |              |    |
|-------------------------------------------------------------------------|--------------|--------------|----|
| Number of subjects                                                      | 6            | 6            | 34 |
| Age categorical<br>Units: Subjects                                      |              |              |    |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 8.2<br>± 0.8 | 9.3<br>± 0.8 | -  |
| Gender categorical<br>Units:                                            |              |              |    |
| Male                                                                    | 2            | 3            | 11 |
| Female                                                                  | 4            | 3            | 23 |
| Diagnosis at Screening<br>Units: Subjects                               |              |              |    |
| NDO                                                                     | 2            | 2            | 11 |
| OAB                                                                     | 4            | 4            | 23 |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                   | Adolescents Low Dose (Fed)  |
| Reporting group description:<br>Adolescents aged 12 to less than 18 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 55.0 kg received 25 mg mirabegron; participants $\geq$ 55.0 kg received 50 mg (both referred to as low dose, predicted to achieve the low exposure target).                                                                                              |                             |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                   | Children Low Dose (Fed)     |
| Reporting group description:<br>Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 55.0 kg received 25 mg mirabegron; participants $\geq$ 55.0 kg received 50 mg (both referred to as low dose, predicted to achieve the low exposure target).                                                                                                  |                             |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                   | Adolescents High Dose (Fed) |
| Reporting group description:<br>Adolescents aged 12 to less than 18 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants $\geq$ 40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).                                                              |                             |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                   | Children High Dose (Fed)    |
| Reporting group description:<br>Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron after a light breakfast on day 1. Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants $\geq$ 40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target).                                                                  |                             |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                   | Children High Dose (Fasted) |
| Reporting group description:<br>Children aged 5 to less than 12 years received a single, weight-based dose of mirabegron under fasted conditions (fasted from at least midnight the day before until 4 hours after dosing). Participants weighing 20.0 to < 40.0 kg received 50 mg mirabegron; participants $\geq$ 40.0 kg received 75 mg (50 mg tablet + 25 mg tablet) (both referred to as high dose, predicted to achieve the high exposure target). |                             |

### Primary: Area Under the Concentration-Time Curve to Infinity (AUCinf) for Mirabegron

|                                                                                                                                                                                                                                                                                                                                                                 |                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                 | Area Under the Concentration-Time Curve to Infinity (AUCinf) for Mirabegron <sup>[1]</sup> |
| End point description:<br>The analysis population was the pharmacokinetic analysis set (PKAS), which consisted of all participants who received the dose of study drug and who had concentration values for a sufficient number of timepoints to reliably calculate at least 1 pharmacokinetic parameter.                                                       |                                                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                  | Primary                                                                                    |
| End point timeframe:<br>Days 1-7: Adolescents [5 samples on day 1&2]: 0.5-2, 3-4, 5-6, 7-8, 24-32 h postdose; Children [4 samples on day 1&2]: 0.5-2, 3-5, 6-8, 24-32 h post dose; All [2 samples from days 3-7]: 48-56, 72-80, or 96-104 h postdose/72-80,120-128 or 144-152 h postdose                                                                        |                                                                                            |
| Notes:<br>[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.<br>Justification: This study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study. |                                                                                            |

| End point values                     | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|--------------------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type                   | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed          | 5 <sup>[2]</sup>           | 7                       | 8                           | 5 <sup>[3]</sup>         |
| Units: ng*h/mL                       |                            |                         |                             |                          |
| arithmetic mean (standard deviation) | 90.83 (± 25.56)            | 128.8 (± 65.48)         | 394.9 (± 205.5)             | 596.5 (± 385.5)          |

Notes:

[2] - Participants with available data.

[3] - Participants with available data.

| End point values                     | Children High Dose (Fasted) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 6                           |  |  |  |
| Units: ng*h/mL                       |                             |  |  |  |
| arithmetic mean (standard deviation) | 830.4 (± 384.8)             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Maximum Concentration (Cmax) of Mirabegron

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Maximum Concentration (Cmax) of Mirabegron <sup>[4]</sup> |
|-----------------|-----------------------------------------------------------|

End point description:

The analysis population was the PKAS.

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

End point timeframe:

Days 1-7:Adolescents [5 samples on day 1&2]: 0.5-2, 3-4, 5-6, 7-8, 24-32 h postdose; Children [4 samples on day 1&2]: 0.5-2, 3-5, 6-8, 24-32 h post dose; All [2 samples from days 3-7]: 48-56, 72-80, or 96-104 h postdose/72-80,120-128 or 144-152 h postdose

Notes:

[4] - 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 study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

| End point values                     | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|--------------------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type                   | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed          | 7                          | 7                       | 8                           | 6                        |
| Units: ng/mL                         |                            |                         |                             |                          |
| arithmetic mean (standard deviation) | 4.73 (± 2.717)             | 6.909 (± 4.67)          | 31.98 (± 26.1)              | 43.99 (± 31.93)          |

| End point values | Children High Dose (Fasted) |  |  |  |
|------------------|-----------------------------|--|--|--|
|------------------|-----------------------------|--|--|--|

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 6               |  |  |  |
| Units: ng/mL                         |                 |  |  |  |
| arithmetic mean (standard deviation) | 56.42 (± 17.73) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Time at Which Cmax Occurred (tmax) for Mirabegron

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Time at Which Cmax Occurred (tmax) for Mirabegron <sup>[5]</sup> |
|-----------------|------------------------------------------------------------------|

End point description:

The analysis population was the PKAS.

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

End point timeframe:

Days 1-7: Adolescents [5 samples on day 1&2]: 0.5-2, 3-4, 5-6, 7-8, 24-32 h postdose; Children [4 samples on day 1&2]: 0.5-2, 3-5, 6-8, 24-32 h post dose; All [2 samples from days 3-7]: 48-56, 72-80, or 96-104 h postdose/72-80, 120-128 or 144-152 h postdose

Notes:

[5] - 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 study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

| End point values              | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|-------------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type            | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed   | 7                          | 7                       | 8                           | 6                        |
| Units: hours                  |                            |                         |                             |                          |
| median (full range (min-max)) | 5.03 (3.95 to 5.75)        | 4.17 (2.55 to 6.37)     | 4.475 (3.08 to 7.08)        | 4.28 (3.88 to 4.42)      |

| End point values              | Children High Dose (Fasted) |  |  |  |
|-------------------------------|-----------------------------|--|--|--|
| Subject group type            | Reporting group             |  |  |  |
| Number of subjects analysed   | 6                           |  |  |  |
| Units: hours                  |                             |  |  |  |
| median (full range (min-max)) | 3.95 (3.47 to 4.27)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Elimination Half Life (t<sub>1/2</sub>) of Mirabegron

|                                                                                                                                                                                                                                                                                         |                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                         | Elimination Half Life (t1/2) of Mirabegron <sup>[6]</sup> |
| End point description:<br>The analysis population was the PKAS.                                                                                                                                                                                                                         |                                                           |
| End point type                                                                                                                                                                                                                                                                          | Primary                                                   |
| End point timeframe:<br>Days 1-7:Adolescents [5 samples on day 1&2]: 0.5-2, 3-4, 5-6, 7-8, 24-32 h postdose; Children [4 samples on day 1&2]: 0.5-2, 3-5, 6-8, 24-32 h post dose; All [2 samples from days 3-7]: 48-56, 72-80, or 96-104 h postdose/72-80,120-128 or 144-152 h postdose |                                                           |

Notes:

[6] - 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 study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

| End point values                     | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|--------------------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type                   | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed          | 5 <sup>[7]</sup>           | 7                       | 8                           | 5 <sup>[8]</sup>         |
| Units: hours                         |                            |                         |                             |                          |
| arithmetic mean (standard deviation) | 27.16 (± 6.664)            | 30.76 (± 8.119)         | 29.2 (± 4.51)               | 28.97 (± 6.076)          |

Notes:

[7] - Participants with available data.

[8] - Participants with available data.

| End point values                     | Children High Dose (Fasted) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 6                           |  |  |  |
| Units: hours                         |                             |  |  |  |
| arithmetic mean (standard deviation) | 26.16 (± 2.931)             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Oral Clearance (CL/F) for Mirabegron

|                                                                                                                                                                                                                                                                                         |                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                         | Apparent Oral Clearance (CL/F) for Mirabegron <sup>[9]</sup> |
| End point description:<br>The analysis population was the PKAS.                                                                                                                                                                                                                         |                                                              |
| End point type                                                                                                                                                                                                                                                                          | Primary                                                      |
| End point timeframe:<br>Days 1-7:Adolescents [5 samples on day 1&2]: 0.5-2, 3-4, 5-6, 7-8, 24-32 h postdose; Children [4 samples on day 1&2]: 0.5-2, 3-5, 6-8, 24-32 h post dose; All [2 samples from days 3-7]: 48-56, 72-80, or 96-104 h postdose/72-80,120-128 or 144-152 h postdose |                                                              |

Notes:

[9] - 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 study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

| End point values                     | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|--------------------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type                   | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed          | 5 <sup>[10]</sup>          | 7                       | 8                           | 5 <sup>[11]</sup>        |
| Units: L/h                           |                            |                         |                             |                          |
| arithmetic mean (standard deviation) | 339.1 (± 97.54)            | 248.7 (± 132.5)         | 230.1 (± 137.4)             | 113 (± 62.89)            |

Notes:

[10] - Participants with available data.

[11] - Participants with available data.

| End point values                     | Children High Dose (Fasted) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 6                           |  |  |  |
| Units: L/h                           |                             |  |  |  |
| arithmetic mean (standard deviation) | 79.08 (± 45.64)             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Apparent Volume of Distribution (V<sub>z</sub>/F) of Mirabegron

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Apparent Volume of Distribution (V <sub>z</sub> /F) of Mirabegron <sup>[12]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

The analysis population was the PKAS.

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

End point timeframe:

Days 1-7:Adolescents [5 samples on day 1&2]: 0.5-2, 3-4, 5-6, 7-8, 24-32 h postdose; Children [4 samples on day 1&2]: 0.5-2, 3-5, 6-8, 24-32 h post dose; All [2 samples from days 3-7]: 48-56, 72-80, or 96-104 h postdose/72-80,120-128 or 144-152 h postdose

Notes:

[12] - 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 study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

| End point values                     | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|--------------------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type                   | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed          | 5 <sup>[13]</sup>          | 7                       | 8                           | 5 <sup>[14]</sup>        |
| Units: liters                        |                            |                         |                             |                          |
| arithmetic mean (standard deviation) | 13063 (± 4569)             | 9959 (± 3639)           | 9918 (± 6702)               | 4895 (± 2921)            |

Notes:

[13] - Participants with available data.

[14] - Participants with available data.

| End point values | Children High Dose (Fasted) |  |  |  |
|------------------|-----------------------------|--|--|--|
|------------------|-----------------------------|--|--|--|

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 6                  |  |  |  |
| Units: liters                        |                    |  |  |  |
| arithmetic mean (standard deviation) | 2866 ( $\pm$ 1438) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Area Under the Concentration-Time Curve to 24 Hours (AUC24) for Mirabegron

|                 |                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Area Under the Concentration-Time Curve to 24 Hours (AUC24) for Mirabegron <sup>[15]</sup> |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

The analysis population was the PKAS.

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

End point timeframe:

Time Frame: Days 1-2: Adolescents [5 samples on day 1&2]: 0.5-2, 3-4, 5-6, 7-8, 24-32 h postdose;  
Children [4 samples on day 1&2]: 0.5-2, 3-5, 6-8, 24-32 h post dose

Notes:

[15] - 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 study was written with no planned statistical analyses (inferential) to be performed for any end points due to the simple design and purpose of the study.

| End point values                     | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|--------------------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type                   | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed          | 7                          | 7                       | 8                           | 6                        |
| Units: ng*h/mL                       |                            |                         |                             |                          |
| arithmetic mean (standard deviation) | 47.9 ( $\pm$ 14.24)        | 66.33 ( $\pm$ 31.66)    | 230.7 ( $\pm$ 132.5)        | 336 ( $\pm$ 225.4)       |

| End point values                     | Children High Dose (Fasted) |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 6                           |  |  |  |
| Units: ng*h/mL                       |                             |  |  |  |
| arithmetic mean (standard deviation) | 508.6 ( $\pm$ 190.2)        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adverse Events (AEs)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Number of Participants with Adverse Events (AEs) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                  |
| Safety was assessed by collecting AEs, which included abnormalities identified during a medical test (e.g. laboratory tests, vital sign, electrocardiogram, etc.) if the abnormality induced clinical signs or symptoms, needed active intervention, interruption or discontinuation of study medication or was clinically significant. A serious AE (SAE) was an event resulting in death, persistent or significant disability/incapacity or congenital anomaly or birth defect, was life-threatening, required or prolonged hospitalization or was considered medically important. A treatment-emergent adverse event (TEAE) was defined as an AE that occurred after administration of the first dose of study drug until 7 days after the last dose of study drug. A related SAE or TEAE was possible or probable, as assessed by the Investigator, or records where relationship is missing. The analysis population was the Safety Analysis Set (SAF) which consisted of all participants who took the dose of study drug. |                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Secondary                                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                  |
| From dosing up to 7 days postdose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                  |

| End point values            | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) | Children High Dose (Fed) |
|-----------------------------|----------------------------|-------------------------|-----------------------------|--------------------------|
| Subject group type          | Reporting group            | Reporting group         | Reporting group             | Reporting group          |
| Number of subjects analysed | 7                          | 7                       | 8                           | 6                        |
| Units: participants         |                            |                         |                             |                          |
| TEAE                        | 1                          | 1                       | 1                           | 0                        |
| Related TEAE                | 0                          | 0                       | 1                           | 0                        |
| Death                       | 0                          | 0                       | 0                           | 0                        |
| SAE                         | 0                          | 0                       | 0                           | 0                        |
| Drug-related SAE            | 0                          | 0                       | 0                           | 0                        |

| End point values            | Children High Dose (Fasted) |  |  |  |
|-----------------------------|-----------------------------|--|--|--|
| Subject group type          | Reporting group             |  |  |  |
| Number of subjects analysed | 6                           |  |  |  |
| Units: participants         |                             |  |  |  |
| TEAE                        | 1                           |  |  |  |
| Related TEAE                | 0                           |  |  |  |
| Death                       | 0                           |  |  |  |
| SAE                         | 0                           |  |  |  |
| Drug-related SAE            | 0                           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From dosing up to 7 days postdose

Adverse event reporting additional description:

SAF

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Adolescents Low Dose (Fed) |
|-----------------------|----------------------------|

Reporting group description:

Male and female adolescents aged 12 to less than 18 years) who received a low dose of mirabegron under fed conditons.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Children Low Dose (Fed) |
|-----------------------|-------------------------|

Reporting group description:

Male and female children aged 5 to less than 12 years who received a low dose of mirabegron under fed conditons.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Adolescents High Dose (Fed) |
|-----------------------|-----------------------------|

Reporting group description:

Male and female adolescents aged 12 to less than 18 years) who received a high dose of mirabegron under fed conditons.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Children High Dose (Fed) |
|-----------------------|--------------------------|

Reporting group description:

Male and female children aged 5 to less than 12 years who received a high dose of mirabegron under fed conditons.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Children High Dose (Fasted) |
|-----------------------|-----------------------------|

Reporting group description:

Male and female children aged 5 to less than 12 years who received a high dose of mirabegron under fasted conditons (fasted from at least midnight the day before before until 4 hours after dosing).

| Serious adverse events                            | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) |
|---------------------------------------------------|----------------------------|-------------------------|-----------------------------|
| Total subjects affected by serious adverse events |                            |                         |                             |
| subjects affected / exposed                       | 0 / 7 (0.00%)              | 0 / 7 (0.00%)           | 0 / 8 (0.00%)               |
| number of deaths (all causes)                     | 0                          | 0                       | 0                           |
| number of deaths resulting from adverse events    | 0                          | 0                       | 0                           |

| Serious adverse events                            | Children High Dose (Fed) | Children High Dose (Fasted) |  |
|---------------------------------------------------|--------------------------|-----------------------------|--|
| Total subjects affected by serious adverse events |                          |                             |  |
| subjects affected / exposed                       | 0 / 6 (0.00%)            | 0 / 6 (0.00%)               |  |
| number of deaths (all causes)                     | 0                        | 0                           |  |
| number of deaths resulting from adverse events    | 0                        | 0                           |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                                                                   | Adolescents Low Dose (Fed) | Children Low Dose (Fed) | Adolescents High Dose (Fed) |
|---------------------------------------------------------------------------------------------------------------------|----------------------------|-------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                | 1 / 7 (14.29%)             | 1 / 7 (14.29%)          | 1 / 8 (12.50%)              |
| Investigations<br>Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)                | 0 / 7 (0.00%)<br>0         | 1 / 7 (14.29%)<br>1     | 1 / 8 (12.50%)<br>1         |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 1 / 7 (14.29%)<br>1        | 0 / 7 (0.00%)<br>0      | 0 / 8 (0.00%)<br>0          |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 7 (14.29%)<br>1        | 0 / 7 (0.00%)<br>0      | 0 / 8 (0.00%)<br>0          |

| <b>Non-serious adverse events</b>                                                                                   | Children High Dose (Fed) | Children High Dose (Fasted) |  |
|---------------------------------------------------------------------------------------------------------------------|--------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                | 0 / 6 (0.00%)            | 1 / 6 (16.67%)              |  |
| Investigations<br>Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)                | 0 / 6 (0.00%)<br>0       | 0 / 6 (0.00%)<br>0          |  |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0       | 0 / 6 (0.00%)<br>0          |  |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 6 (0.00%)<br>0       | 1 / 6 (16.67%)<br>1         |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 September 2014 | In this global amendment, changes include: (1) The United States was added as a study location; (2) The method for estimated glomerular filtration rate calculation was amended from the modification of diet in renal disease (MDRD) study equation method to the revised Schwartz method; (3) Cystatin C was added as a biochemistry parameter.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 06 February 2015  | In this global amendment, changes include: (1) The Investigator's Brochure was listed as a source for contraindications or precautions to exclusion criterion 12; (2) The required wash-out period for mirabegron before the planned reference day (day -4 to day -1) was amended from 24 days to 12 days; (3) Current, untreated constipation (or fecal impaction for NDO participants) were added as an exclusion criterion at screening; (4) Use of botox within 4 months prior to screening was added as an exclusion criterion at screening; (5) Symptomatic Urinary tract infection (UTI) was added as a day 1 exclusion criterion; (6) Several sections were updated to allow preselected study visits to take place outside the clinic; (7) The pharmacokinetic-specific restrictions for dosing on Friday and weekend samplings were removed; (8) Assessments of palatability (taste) and acceptability (ease of swallowing) were included in the protocol as exploratory endpoints. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported