



## Clinical trial results:

**A phase 3, randomised, double-blind, multicentre, parallel-group, placebo- and active-reference, dose-optimisation efficacy and safety study of extended-release Guanfacine Hydrochloride in children and adolescents aged 6-17 years with Attention-Deficit/Hyperactivity Disorder**

### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2010-018579-12                |
| Trial protocol           | GB DE NL FR ES SE IE AT BG IT |
| Global end of trial date | 01 May 2013                   |

### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 25 November 2018  |
| First version publication date | 01 May 2015   |
| Version creation reason        | • Correction of full data set<br>Updated upper limit of one statistical analysis. |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | SPD503-316 |
|-----------------------|------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01244490 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Shire Pharmaceutical Development Ltd.  |
| Sponsor organisation address | Hampshire International Business Park, Chineham,<br>Basingstoke, Hampshire, United Kingdom, RG24 8EP |
| Public contact               | Shire Development LLC, Study Physician, +1 866 842 5335 ,  |
| Scientific contact           | Shire Development LLC, Study Physician, +1 866 842 5335 ,  |

Notes:

### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000745-PIP01-09 |
| 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? | No                  |

Notes:

## Results analysis stage

|  |             |
|--|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 01 May 2013 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 01 May 2013 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of once daily dosing with optimised SPD503 compared to placebo in the treatment of children and adolescents aged 6-17 years with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) as measured by the ADHD Rating Scale-IV (ADHD-RS-IV).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements. The subject's informed consent and assent (as applicable) were mandatory for taking part in the study. It was obtained in writing prior to the performance of any study-specific procedures.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 17 January 2011 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 37        |
| Country: Number of subjects enrolled | Romania: 14       |
| Country: Number of subjects enrolled | Spain: 51         |
| Country: Number of subjects enrolled | Sweden: 4         |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Austria: 11       |
| Country: Number of subjects enrolled | France: 6         |
| Country: Number of subjects enrolled | Germany: 68       |
| Country: Number of subjects enrolled | Ireland: 2        |
| Country: Number of subjects enrolled | Italy: 13         |
| Country: Number of subjects enrolled | Ukraine: 54       |
| Country: Number of subjects enrolled | Canada: 19        |
| Country: Number of subjects enrolled | United States: 57 |
| Worldwide total number of subjects   | 338               |
| EEA total number of subjects         | 208               |

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)                     | 204 |
| Adolescents (12-17 years)                 | 134 |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited to participate at 1 of 58 sites, including 11 sites in the United States (US), 2 sites in Canada, and 45 sites in Europe (Austria, France, Germany, Ireland, Italy, Poland, Romania, Spain, Sweden, Ukraine, and United Kingdom).

### Pre-assignment

Screening details:

This study consisted of a screening/washout period that lasted for 35 days. Following successful screening, the subject discontinued any current psychoactive medication (if any) for the Washout Period. The washout for all prohibited medications was at least a minimum of 5 times the half-life of the medication.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

Blinding implementation details:

Capsules were overencapsulated to protect the blind between the active product and the placebo.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.

|  |                |
|--|----------------|
| Arm type                               | Placebo        |
| Investigational medicinal product name | SPD503 Placebo |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

Dosage and administration details:

Subjects were to take 1 matching placebo tablet once daily if optimized to a dose of 1-4mg SPD503 or 2 matching placebo tablets once daily if optimized to a dose of 5-7mg SPD503.

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Strattera Placebo |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Capsule           |
| Routes of administration               | Oral use          |

Dosage and administration details:

Subjects optimized to a dose requiring a daily dose higher than 60mg of STRATTERA took 2 matching placebo capsules once daily. Subjects at all other optimized doses ( $\leq$  60mg/day) took 1 matching placebo capsule once daily.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Guanfacine Hydrochloride |
|------------------|--------------------------|

Arm description:

Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.

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

|  |                          |
|--|--------------------------|
| Investigational medicinal product name | Guanfacine Hydrochloride |
| Investigational medicinal product code |                          |
| Other name                             | SPD503, Intuniv          |
| Pharmaceutical forms                   | Tablet                   |
| Routes of administration               | Oral use                 |

Dosage and administration details:

A combination of 1, 2, 3, and 4mg tablets for a total dosage of 1mg to 7mg based on age and weight. Subjects were to take either 1 SPD503 tablet once daily if optimized to a dose of 1-4mg or 2 SPD503 tablets once daily if optimized to a dose of 5-7mg.

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Strattera Placebo |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Capsule           |
| Routes of administration               | Oral use          |

Dosage and administration details:

Subjects optimized to a dose requiring a daily dose higher than 60mg of STRATTERA took 2 matching placebo capsules once daily. Subjects at all other optimized doses ( $\leq$  60mg/day) took 1 matching placebo capsule once daily.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Atomoxetine Hydrochloride |
|------------------|---------------------------|

Arm description:

Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo.

|  |                           |
|--|---------------------------|
| Arm type                               | Active comparator         |
| Investigational medicinal product name | Atomoxetine Hydrochloride |
| Investigational medicinal product code |                           |
| Other name                             | Strattera                 |
| Pharmaceutical forms                   | Capsule                   |
| Routes of administration               | Oral use                  |

Dosage and administration details:

A combination of 10, 18, 25, 40, or 60mg capsules, once daily, at the optimised dose (10mg to 100mg based on weight). The maximum dose was 4mg/day for children aged 6-12 years and 4-7mg/day for adolescents aged 13-17 years, depending on the subject's weight. Subjects optimized to a dose requiring a daily dose higher than 60mg took 2 STRATTERA capsules. Subjects at all other optimized doses ( $\leq$  60mg/day) took 1 STRATTERA capsule.

|  |                |
|--|----------------|
| Investigational medicinal product name | SPD503 Placebo |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Tablet         |
| Routes of administration               | Oral use       |

Dosage and administration details:

Subjects were to take 1 matching placebo tablet once daily if optimized to a dose of 1-4mg SPD503 or 2 matching placebo tablets once daily if optimized to a dose of 5-7mg SPD503.

| <b>Number of subjects in period 1</b> | Placebo | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |
|---------------------------------------|---------|--------------------------|---------------------------|
| Started                               | 111     | 115                      | 112                       |
| Completed                             | 92      | 91                       | 89                        |
| Not completed                         | 19      | 24                       | 23                        |
| Not specified                         | -       | -                        | 1                         |
| Adverse event                         | 1       | 9                        | 5                         |
| Lost to follow-up                     | -       | 6                        | 3                         |

|                       |    |   |   |
|-----------------------|----|---|---|
| Lack of efficacy      | 14 | 5 | 5 |
| Withdrawal by subject | 4  | 4 | 9 |

## Baseline characteristics

### Reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Placebo                   |
| Reporting group description:   |                           |
| Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.                  |                           |
| Reporting group title  | Guanfacine Hydrochloride  |
| Reporting group description:   |                           |
| Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.  |                           |
| Reporting group title  | Atomoxetine Hydrochloride |
| Reporting group description:   |                           |
| Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo. |                           |

| Reporting group values | Placebo | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |
|------------------------|---------|--------------------------|---------------------------|
| Number of subjects     | 111     | 115                      | 112                       |
| Age categorical        |         |                          |                           |
| Units: Subjects        |         |                          |                           |
| 6-12 years             | 79      | 81                       | 82                        |
| 13-17 years            | 32      | 34                       | 30                        |
| Age continuous         |         |                          |                           |
| Units: years           |         |                          |                           |
| arithmetic mean        | 11      | 10.9                     | 10.5                      |
| standard deviation     | ± 2.76  | ± 2.78                   | ± 2.81                    |
| Gender categorical     |         |                          |                           |
| Units: Subjects        |         |                          |                           |
| Female                 | 25      | 38                       | 25                        |
| Male                   | 86      | 77                       | 87                        |
| Region of enrollment   |         |                          |                           |
| Units: Subjects        |         |                          |                           |
| Austria                | 2       | 4                        | 5                         |
| Canada                 | 6       | 7                        | 6                         |
| France                 | 2       | 2                        | 2                         |
| Germany                | 23      | 23                       | 22                        |
| Ireland                | 0       | 1                        | 1                         |
| Italy                  | 5       | 4                        | 4                         |
| Poland                 | 11      | 14                       | 12                        |
| Romania                | 5       | 3                        | 6                         |
| Spain                  | 16      | 18                       | 17                        |
| Sweden                 | 1       | 1                        | 2                         |
| Ukraine                | 21      | 18                       | 15                        |
| United Kingdom         | 1       | 0                        | 1                         |
| United States          | 18      | 20                       | 19                        |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 338   |  |  |
| Age categorical        |       |  |  |
| Units: Subjects        |       |  |  |
| 6-12 years             | 242   |  |  |

|             |    |  |  |
|-------------|----|--|--|
| 13-17 years | 96 |  |  |
|-------------|----|--|--|

|   |     |  |  |
|---|-----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -   |  |  |
| Gender categorical<br>Units: Subjects                                   |     |  |  |
| Female  | 88  |  |  |
| Male  | 250 |  |  |
| Region of enrollment<br>Units: Subjects                                 |     |  |  |
| Austria   | 11  |  |  |
| Canada  | 19  |  |  |
| France  | 6   |  |  |
| Germany   | 68  |  |  |
| Ireland   | 2   |  |  |
| Italy   | 13  |  |  |
| Poland  | 37  |  |  |
| Romania   | 14  |  |  |
| Spain   | 51  |  |  |
| Sweden  | 4   |  |  |
| Ukraine   | 54  |  |  |
| United Kingdom  | 2   |  |  |
| United States   | 57  |  |  |



## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Placebo                   |
| Reporting group description:<br>Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.                  |                           |
| Reporting group title  | Guanfacine Hydrochloride  |
| Reporting group description:<br>Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.  |                           |
| Reporting group title  | Atomoxetine Hydrochloride |
| Reporting group description:<br>Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo. |                           |

### Primary: Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 10/13 - Last Observation Carried Forward (LOCF)

|   |   |
|---|---|
| End point title   | Change From Baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth Edition (ADHD-RS-IV) Total Score at Week 10/13 - Last Observation Carried Forward (LOCF) |
| End point description:<br>The ADHD-RS-IV consists of 18 items scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms) with total score ranging from 0 to 54. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.<br>This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 20% of the items used for summing a score were missing, the score was set to missing. |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years  |   |

| End point values                    | Placebo         | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|-----------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 111             | 112                      | 112                       |  |
| Units: units on a scale             |                 |                          |                           |  |
| least squares mean (standard error) | -15 (± 1.1612)  | -23.9 (± 1.1531)         | -18.8 (± 1.1549)          |  |

### Statistical analyses

|                            |                                    |
|----------------------------|------------------------------------|
| Statistical analysis title | Analysis of ADHD-RS-IV total score |
| Comparison groups          | Placebo v Guanfacine Hydrochloride |

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 223                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | < 0.001                          |
| Method                                  | ANCOVA                           |
| Parameter estimate                      | Difference in least squares mean |
| Point estimate                          | -8.9                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -11.9                            |
| upper limit                             | -5.8                             |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of ADHD-RS-IV total score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride   |
| Number of subjects included in analysis | 223                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.017                               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | Difference in least squares mean      |
| Point estimate                          | -3.8                                  |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -6.8                                  |
| upper limit                             | -0.7                                  |

### **Secondary: Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Score**

|                 |  |
|-----------------|--|
| End point title | Percent of Subjects With Improvement on Clinical Global Impression-Improvement (CGI-I) Score |
|-----------------|--|

#### **End point description:**

Clinical Global Impression-Improvement (CGI-I) consists of a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved) or 2 (much improved) on the scale. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. Not all subjects in the FAS population had data for this outcome.

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

#### **End point timeframe:**

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| <b>End point values</b>     | Placebo         | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-----------------------------|-----------------|--------------------------|---------------------------|--|
| Subject group type          | Reporting group | Reporting group          | Reporting group           |  |
| Number of subjects analysed | 111             | 112                      | 112                       |  |
| Units: percent of subjects  |                 |                          |                           |  |
| number (not applicable)     | 44.1            | 67.9                     | 56.3                      |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of CGI-I score              |
| Comparison groups                       | Placebo v Guanfacine Hydrochloride   |
| Number of subjects included in analysis | 223                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | < 0.001                              |
| Method                                  | Cochran-Mantel-Haenszel              |
| Parameter estimate                      | Difference in percentage improvement |
| Point estimate                          | 23.7                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 11.1                                 |
| upper limit                             | 36.4                                 |

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of CGI-I score #2           |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride  |
| Number of subjects included in analysis | 223                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | = 0.024                              |
| Method                                  | Cochran-Mantel-Haenszel              |
| Parameter estimate                      | Difference in percentage improvement |
| Point estimate                          | 12.1                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.9                                 |
| upper limit                             | 25.1                                 |

## Secondary: Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Learning and School Domain Score at Week 10/13 - LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) Learning and School Domain Score at Week 10/13 - LOCF |
|-----------------|--|

---

**End point description:**

The WFIRS-P Learning in School Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

---

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

---

**End point timeframe:**

Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

---

| End point values                    | Placebo                | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|------------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group        | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 100                    | 103                      | 100                       |  |
| Units: units on a scale             |                        |                          |                           |  |
| least squares mean (standard error) | -0.419 ( $\pm$ 0.0537) | -0.636 ( $\pm$ 0.0527)   | -0.581 ( $\pm$ 0.0534)    |  |

**Statistical analyses**

| Statistical analysis title              | Analysis of WFIRS-P learning domain score |
|---|---|
| Comparison groups                       | Placebo v Guanfacine Hydrochloride        |
| Number of subjects included in analysis | 203                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.003                                   |
| Method                                  | ANCOVA                                    |
| Parameter estimate                      | Difference in least squares mean          |
| Point estimate                          | -0.217                                    |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -0.358                                    |
| upper limit                             | -0.076                                    |

---

| Statistical analysis title | Analysis of WFIRS-P learning domain score #2 |
|----------------------------|--|
| Comparison groups          | Placebo v Atomoxetine Hydrochloride          |

---

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 200                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.026                          |
| Method                                  | ANCOVA                           |
| Parameter estimate                      | Difference in least squares mean |
| Point estimate                          | -0.162                           |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -0.305                           |
| upper limit                             | -0.019                           |

## Secondary: Change From Baseline in the WFIRS-P Family Domain Score at Week 10/13 - LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the WFIRS-P Family Domain Score at Week 10/13 - LOCF |
|-----------------|--|

End point description:

The WFIRS-P Family Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

End point timeframe:

Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                    | Placebo           | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|-------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group   | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 106               | 109                      | 105                       |  |
| Units: units on a scale             |                   |                          |                           |  |
| least squares mean (standard error) | -0.409 (± 0.0568) | -0.617 (± 0.0558)        | -0.499 (± 0.0566)         |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Analysis of WFIRS-P family domain score |
| Comparison groups          | Placebo v Guanfacine Hydrochloride      |

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 215                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.006                          |
| Method                                  | ANCOVA                           |
| Parameter estimate                      | Difference in least squares mean |
| Point estimate                          | -0.209                           |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -0.358                           |
| upper limit                             | -0.059                           |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P family domain score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride        |
| Number of subjects included in analysis | 211  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.242                                    |
| Method                                  | ANCOVA                                     |
| Parameter estimate                      | Difference in least squares mean           |
| Point estimate                          | -0.09                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -0.241                                     |
| upper limit                             | 0.061                                      |

## Secondary: Clinical Global Impression-Severity of Illness (CGI-S) - LOCF

|   |   |
|---|---|
| End point title   | Clinical Global Impression-Severity of Illness (CGI-S) - LOCF |
| End point description:  |   |
| CGI-S assesses the severity of the subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years. |   |
| This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. Not all subjects in the FAS population had data for this outcome.                                   |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years   |   |

| End point values                 | Placebo         | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|----------------------------------|-----------------|--------------------------|---------------------------|--|
| Subject group type               | Reporting group | Reporting group          | Reporting group           |  |
| Number of subjects analysed      | 111             | 112                      | 112                       |  |
| Units: percent of subjects       |                 |                          |                           |  |
| number (not applicable)          |                 |                          |                           |  |
| 1 (Normal, not at all ill)       | 9.9             | 14.3                     | 6.3                       |  |
| 2 (Borderline mentally ill)      | 15.3            | 23.2                     | 19.6                      |  |
| 3 (Mildly ill)                   | 20.7            | 31.3                     | 32.1                      |  |
| 4 (Moderately ill)               | 20.7            | 22.3                     | 19.6                      |  |
| 5 (Markedly ill)                 | 25.2            | 5.4                      | 13.4                      |  |
| 6 (Severely ill)                 | 6.3             | 3.6                      | 7.1                       |  |
| 7 (Among the most extremely ill) | 1.8             | 0                        | 1.8                       |  |

### Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of CGI-S                  |
| Comparison groups                       | Placebo v Guanfacine Hydrochloride |
| Number of subjects included in analysis | 223                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | < 0.001 <sup>[1]</sup>             |
| Method                                  | Cochran-Mantel-Haenszel            |

Notes:

[1] - Nominal p-value uncorrected for multiplicity.

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of CGI-S #2                |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride |
| Number of subjects included in analysis | 223                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.196 <sup>[2]</sup>              |
| Method                                  | Cochran-Mantel-Haenszel             |

Notes:

[2] - Nominal p-value uncorrected for multiplicity.

### Secondary: Health Utilities Index-2/3 (HUI 2/3) Scores - LOCF

|  |  |
|--|--|
| <b>End point title</b>   | Health Utilities Index-2/3 (HUI 2/3) Scores - LOCF |
| End point description:   |  |
| HUI is used to describe health status and to obtain utility scores by collecting data using one or more questionnaires in formats selected to match the specific study design criteria. Scoring ranges from 0.00 (dead) to 1.00 (perfect health). Higher scores represent better health status. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years. This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. Not all subjects in the FAS population had data for this outcome. |  |
| <b>End point type</b>  | Secondary  |

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                     | Placebo              | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|--------------------------------------|----------------------|--------------------------|---------------------------|--|
| Subject group type                   | Reporting group      | Reporting group          | Reporting group           |  |
| Number of subjects analysed          | 106                  | 110                      | 106                       |  |
| Units: units on a scale              |                      |                          |                           |  |
| arithmetic mean (standard deviation) | 0.927 ( $\pm$ 0.095) | 0.922 ( $\pm$ 0.0908)    | 0.913 ( $\pm$ 0.1052)     |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the WFIRS-P Global Score at Week 10/13 - LOCF

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in the WFIRS-P Global Score at Week 10/13 - LOCF |
|-----------------|---|

End point description:

The WFIRS-P Global Score is the mean of 50 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

End point timeframe:

Baseline and Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                    | Placebo                | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|------------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group        | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 104                    | 110                      | 104                       |  |
| Units: units on a scale             |                        |                          |                           |  |
| least squares mean (standard error) | -0.321 ( $\pm$ 0.0387) | -0.487 ( $\pm$ 0.0374)   | -0.425 ( $\pm$ 0.0384)    |  |

## Statistical analyses

|                            |                                    |
|----------------------------|------------------------------------|
| Statistical analysis title | Analysis of WFIRS-P global score   |
| Comparison groups          | Placebo v Guanfacine Hydrochloride |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 214                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.001 <sup>[3]</sup>         |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.165                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.266                         |
| upper limit                             | -0.064                         |

Notes:

[3] - Nominal p-value uncorrected for multiplicity.

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P global score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride |
| Number of subjects included in analysis | 208                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.048 <sup>[4]</sup>              |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | -0.104                              |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.207                              |
| upper limit                             | -0.001                              |

Notes:

[4] - Nominal p-value uncorrected for multiplicity.

### **Secondary: Change From Baseline in the WFIRS-P Academic Performance Domain Score at Week 10/13 - LOCF**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the WFIRS-P Academic Performance Domain Score at Week 10/13 - LOCF |
|-----------------|--|

End point description:

The WFIRS-P Academic Performance Domain is the mean of 4 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| <b>End point values</b>             | Placebo                | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|------------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group        | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 96                     | 103                      | 101                       |  |
| Units: units on a scale             |                        |                          |                           |  |
| least squares mean (standard error) | -0.555 ( $\pm$ 0.0784) | -0.766 ( $\pm$ 0.0757)   | -0.681 ( $\pm$ 0.0759)    |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P academic performance score |
| Comparison groups                       | Placebo v Guanfacine Hydrochloride             |
| Number of subjects included in analysis | 199  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | = 0.043 <sup>[5]</sup>                         |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Difference in least squares mean               |
| Point estimate                          | -0.211   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.416   |
| upper limit                             | -0.007   |

Notes:

[5] - Nominal p-value uncorrected for multiplicity.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P academic performance score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride               |
| Number of subjects included in analysis | 197   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | superiority                                       |
| P-value                                 | = 0.231 <sup>[6]</sup>                            |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Difference in least squares mean                  |
| Point estimate                          | -0.125  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.331  |
| upper limit                             | 0.08  |

Notes:

[6] - Nominal p-value uncorrected for multiplicity.

### Secondary: Change From Baseline in the WFIRS-P Behavior in School Domain Score at Week 10/13 - LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the WFIRS-P Behavior in School Domain Score at Week 10/13 - LOCF |
|-----------------|--|

**End point description:**

The WFIRS-P Behavior in School Domain is the mean of 6 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

**End point timeframe:**

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                    | Placebo                | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|------------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group        | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 100                    | 103                      | 100                       |  |
| Units: units on a scale             |                        |                          |                           |  |
| least squares mean (standard error) | -0.363 ( $\pm$ 0.0512) | -0.592 ( $\pm$ 0.0502)   | -0.544 ( $\pm$ 0.0509)    |  |

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P school behavior score |
| Comparison groups                       | Placebo v Guanfacine Hydrochloride        |
| Number of subjects included in analysis | 203                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | < 0.001 <sup>[7]</sup>                    |
| Method                                  | ANCOVA                                    |
| Parameter estimate                      | Difference in least squares mean          |
| Point estimate                          | -0.229                                    |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -0.364                                    |
| upper limit                             | -0.094                                    |

**Notes:**

[7] - Nominal p-value uncorrected for multiplicity.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P school behavior score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride          |
| Number of subjects included in analysis | 200  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.009 <sup>[8]</sup>                       |
| Method                                  | ANCOVA                                       |
| Parameter estimate                      | Difference in least squares mean             |
| Point estimate                          | -0.181                                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.317  |
| upper limit         | -0.045  |

Notes:

[8] - Nominal p-value uncorrected for multiplicity.

## Secondary: Change From Baseline in the WFIRS-P Life Skills Domain Score at Week 10/13 - LOCF

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in the WFIRS-P Life Skills Domain Score at Week 10/13 - LOCF |
|-----------------|---|

End point description:

The WFIRS-P Life Skills Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                    | Placebo           | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|-------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group   | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 105               | 110                      | 104                       |  |
| Units: units on a scale             |                   |                          |                           |  |
| least squares mean (standard error) | -0.383 (± 0.0422) | -0.477 (± 0.0411)        | -0.45 (± 0.0422)          |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of WFIRS-P life skills domain score |
| Comparison groups                       | Guanfacine Hydrochloride v Placebo           |
| Number of subjects included in analysis | 215  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.096 <sup>[9]</sup>                       |
| Method                                  | ANCOVA                                       |
| Parameter estimate                      | Difference in least squares mean             |
| Point estimate                          | -0.094                                       |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | -0.204                                       |
| upper limit                             | 0.017  |

Notes:

[9] - Nominal p-value uncorrected for multiplicity.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P life skills domain score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride             |
| Number of subjects included in analysis | 209   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.242 <sup>[10]</sup>                         |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Difference in least squares mean                |
| Point estimate                          | -0.067  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.18   |
| upper limit                             | 0.046   |

Notes:

[10] - Nominal p-value uncorrected for multiplicity.

### **Secondary: Change From Baseline in the WFIRS-P Child Self-Concept Domain Score at Week 10/13 - LOCF**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the WFIRS-P Child Self-Concept Domain Score at Week 10/13 - LOCF |
|-----------------|--|

End point description:

The WFIRS-P Child Self-Concept Domain is the mean of 3 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| <b>End point values</b>             | Placebo           | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|-------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group   | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 101               | 108                      | 103                       |  |
| Units: units on a scale             |                   |                          |                           |  |
| least squares mean (standard error) | -0.312 (± 0.0544) | -0.361 (± 0.0528)        | -0.39 (± 0.0536)          |  |

### **Statistical analyses**

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of WFIRS-P self-concept domain score |
| Comparison groups                 | Placebo v Guanfacine Hydrochloride            |

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 209                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.5 <sup>[11]</sup>            |
| Method                                  | ANCOVA                           |
| Parameter estimate                      | Difference in least squares mean |
| Point estimate                          | -0.049                           |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -0.191                           |
| upper limit                             | 0.094                            |

Notes:

[11] - Nominal p-value uncorrected for multiplicity.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P self-concept domain score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride              |
| Number of subjects included in analysis | 204  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.288 <sup>[12]</sup>                          |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Difference in least squares mean                 |
| Point estimate                          | -0.078   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.222   |
| upper limit                             | 0.066  |

Notes:

[12] - Nominal p-value uncorrected for multiplicity.

### **Secondary: Change From Baseline in the WFIRS-P Social Domain Score at Week 10/13 - LOCF**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the WFIRS-P Social Domain Score at Week 10/13 - LOCF |
|-----------------|--|

End point description:

The WFIRS-P Social Domain is the mean of 7 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

End point timeframe:

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                    | Placebo                | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|------------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group        | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 104                    | 110                      | 104                       |  |
| Units: units on a scale             |                        |                          |                           |  |
| least squares mean (standard error) | -0.322 ( $\pm$ 0.0537) | -0.555 ( $\pm$ 0.0519)   | -0.434 ( $\pm$ 0.0532)    |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P social domain score |
| Comparison groups                       | Placebo v Guanfacine Hydrochloride      |
| Number of subjects included in analysis | 214                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.001 <sup>[13]</sup>                 |
| Method                                  | ANCOVA                                  |
| Parameter estimate                      | Difference in least squares mean        |
| Point estimate                          | -0.233                                  |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.374                                  |
| upper limit                             | -0.092                                  |

Notes:

[13] - Nominal p-value uncorrected for multiplicity.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P social domain score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride        |
| Number of subjects included in analysis | 208  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.124 <sup>[14]</sup>                    |
| Method                                  | ANCOVA                                     |
| Parameter estimate                      | Difference in least squares mean           |
| Point estimate                          | -0.111                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -0.253                                     |
| upper limit                             | 0.031                                      |

Notes:

[14] - Nominal p-value uncorrected for multiplicity.

## Secondary: Change From Baseline in the WFIRS-P Risk Domain Score at Week 10/13 - LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the WFIRS-P Risk Domain Score at Week 10/13 - LOCF |
|-----------------|--|

**End point description:**

The WFIRS-P Risk Domain is the mean of 10 items, ranging from 0 (never/not at all) to 3 (very often/very much). Higher scores indicate greater functional impairment. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Full Analysis Set (FAS), defined as all randomized subjects who took at least 1 dose of investigational product. If more than 30% of items used to derive the score were missing, the corresponding score was considered as missing.

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

**End point timeframe:**

Up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                    | Placebo                | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-------------------------------------|------------------------|--------------------------|---------------------------|--|
| Subject group type                  | Reporting group        | Reporting group          | Reporting group           |  |
| Number of subjects analysed         | 99                     | 105                      | 97                        |  |
| Units: units on a scale             |                        |                          |                           |  |
| least squares mean (standard error) | -0.134 ( $\pm$ 0.0284) | -0.19 ( $\pm$ 0.0275)    | -0.173 ( $\pm$ 0.0285)    |  |

**Statistical analyses**

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P risk domain score |
| Comparison groups                       | Placebo v Guanfacine Hydrochloride    |
| Number of subjects included in analysis | 204                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.139 <sup>[15]</sup>               |
| Method                                  | ANCOVA                                |
| Parameter estimate                      | Difference in least squares mean      |
| Point estimate                          | -0.056                                |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -0.131                                |
| upper limit                             | 0.018                                 |

**Notes:**

[15] - Nominal p-value uncorrected for multiplicity.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of WFIRS-P risk domain score #2 |
| Comparison groups                       | Placebo v Atomoxetine Hydrochloride      |
| Number of subjects included in analysis | 196                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.315 <sup>[16]</sup>                  |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | Difference in least squares mean         |
| Point estimate                          | -0.039                                   |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.115  |
| upper limit         | 0.037   |

Notes:

[16] - Nominal p-value uncorrected for multiplicity.

### Secondary: Change From Baseline in Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Weeks 10/13 - LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Brief Psychiatric Rating Scale for Children (BPRS-C) Total Score at Weeks 10/13 - LOCF |
|-----------------|--|

End point description:

The BPRS-C characterizes childhood behavioral and emotional symptomatology. A total of 21 items are rated on a scale from 0 (not present) to 6 (extremely severe) with a total score ranging from 0 to 126. A decrease in score indicates a reduction in psychopathology. Outcome measure is at 10 weeks for ages 6-12 years and at 13 weeks for ages 13-17 years.

This endpoint analyzed the Safety Population, defined as of randomized subjects who took at least 1 dose of investigational product.

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

End point timeframe:

Baseline and up to 10 weeks for children aged 6-12 years and up to 13 weeks for adolescents aged 13-17 years

| End point values                     | Placebo         | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|--------------------------------------|-----------------|--------------------------|---------------------------|--|
| Subject group type                   | Reporting group | Reporting group          | Reporting group           |  |
| Number of subjects analysed          | 102             | 101                      | 99                        |  |
| Units: units on a scale              |                 |                          |                           |  |
| arithmetic mean (standard deviation) | -5.6 (± 8.82)   | -8.3 (± 8.4)             | -6.5 (± 9.23)             |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Structure Side-Effect Questionnaire

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Structure Side-Effect Questionnaire |
|-----------------|-------------------------------------|

End point description:

The Structured Side-effect Questionnaire is a simple checklist of 17 side effects. The subject indicates whether a side effect has occurred since the last visit by marking 'yes' on the checklist for each of the events listed. Outcome measure is at 12 weeks for ages 6-12 years and at 15 weeks for ages 13-17 years.

This endpoint analyzed the Safety Population, defined as of randomized subjects who took at least 1 dose of investigational product.

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

End point timeframe:

Up to 12 weeks for children aged 6-12 years and up to 15 weeks for adolescents aged 13-17 years

| <b>End point values</b>     | Placebo         | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-----------------------------|-----------------|--------------------------|---------------------------|--|
| Subject group type          | Reporting group | Reporting group          | Reporting group           |  |
| Number of subjects analysed | 111             | 112                      | 112                       |  |
| Units: participants         |                 |                          |                           |  |
| Nausea                      | 19              | 30                       | 39                        |  |
| Vomiting                    | 11              | 7                        | 25                        |  |
| Diarrhea                    | 15              | 18                       | 8                         |  |
| Abdominal Pain              | 26              | 45                       | 42                        |  |
| Decreased Appetite          | 25              | 31                       | 48                        |  |
| Increased Appetite          | 30              | 40                       | 25                        |  |
| Headache                    | 35              | 52                       | 34                        |  |
| Dizziness                   | 16              | 28                       | 23                        |  |
| Fatigue                     | 30              | 55                       | 35                        |  |
| Nervousness/Anxiety         | 25              | 37                       | 34                        |  |
| Insomnia                    | 19              | 32                       | 24                        |  |
| Somnolence                  | 26              | 57                       | 38                        |  |
| Depression                  | 7               | 7                        | 9                         |  |
| Itching                     | 7               | 13                       | 10                        |  |
| Rash                        | 4               | 9                        | 8                         |  |
| Missed Menses               | 0               | 1                        | 0                         |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale (C-SSRS)

|                 |   |
|-----------------|---|
| End point title | Columbia-Suicide Severity Rating Scale (C-SSRS) |
|-----------------|---|

End point description:

C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behaviour occurred. The assessment is done by the nature of the responses, not by a numbered scale. Outcome measure is at 12 weeks for ages 6-12 years and at 15 weeks for ages 13-17 years. This endpoint analyzed the Safety Population, defined as of randomized subjects who took at least 1 dose of investigational product.

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

End point timeframe:

Up to 12 weeks for children aged 6-12 years and up to 15 weeks for adolescents aged 13-17 years

| <b>End point values</b>     | Placebo         | Guanfacine Hydrochloride | Atomoxetine Hydrochloride |  |
|-----------------------------|-----------------|--------------------------|---------------------------|--|
| Subject group type          | Reporting group | Reporting group          | Reporting group           |  |
| Number of subjects analysed | 111             | 112                      | 112                       |  |
| Units: participants         |                 |                          |                           |  |
| Suicidal Ideation           | 2               | 3                        | 5                         |  |
| Suicidal Behaviour          | 0               | 0                        | 0                         |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

13 weeks

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Guanfacine Hydrochloride |
|-----------------------|--------------------------|

Reporting group description:

Subjects randomized to guanfacine hydrochloride received active SPD503 and STRATTERA placebo.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Atomoxetine Hydrochloride |
|-----------------------|---------------------------|

Reporting group description:

Subjects randomized to atomoxetine hydrochloride received active STRATTERA and SPD503 placebo.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects randomized to placebo received SPD503 placebo and STRATTERA placebo.

| Serious adverse events                            | Guanfacine Hydrochloride | Atomoxetine Hydrochloride | Placebo         |
|---|--------------------------|---------------------------|-----------------|
| Total subjects affected by serious adverse events |                          |                           |                 |
| subjects affected / exposed                       | 1 / 114 (0.88%)          | 0 / 112 (0.00%)           | 1 / 111 (0.90%) |
| number of deaths (all causes)                     | 0                        | 0                         | 0               |
| number of deaths resulting from adverse events    | 0                        | 0                         | 0               |
| Nervous system disorders                          |                          |                           |                 |
| Syncope   |                          |                           |                 |
| subjects affected / exposed                       | 1 / 114 (0.88%)          | 0 / 112 (0.00%)           | 1 / 111 (0.90%) |
| occurrences causally related to treatment / all   | 0 / 1                    | 0 / 0                     | 1 / 1           |
| deaths causally related to treatment / all        | 0 / 0                    | 0 / 0                     | 0 / 0           |

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

| Non-serious adverse events                            | Guanfacine Hydrochloride | Atomoxetine Hydrochloride | Placebo           |
|---|--------------------------|---------------------------|-------------------|
| Total subjects affected by non-serious adverse events |                          |                           |                   |
| subjects affected / exposed                           | 79 / 114 (69.30%)        | 67 / 112 (59.82%)         | 62 / 111 (55.86%) |
| Nervous system disorders                              |                          |                           |                   |
| Dizziness   |                          |                           |                   |

|  |                         |                         |                         |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                         | 14 / 114 (12.28%)<br>18 | 17 / 112 (15.18%)<br>24 | 9 / 111 (8.11%)<br>9    |
| Headache<br>subjects affected / exposed<br>occurrences (all)             | 30 / 114 (26.32%)<br>51 | 22 / 112 (19.64%)<br>36 | 27 / 111 (24.32%)<br>46 |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)           | 50 / 114 (43.86%)<br>94 | 20 / 112 (17.86%)<br>32 | 16 / 111 (14.41%)<br>18 |
| General disorders and administration<br>site conditions                  |                         |                         |                         |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)              | 29 / 114 (25.44%)<br>45 | 24 / 112 (21.43%)<br>32 | 20 / 111 (18.02%)<br>22 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)              | 7 / 114 (6.14%)<br>9    | 3 / 112 (2.68%)<br>4    | 4 / 111 (3.60%)<br>4    |
| Gastrointestinal disorders   |                         |                         |                         |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 19 / 114 (16.67%)<br>29 | 19 / 112 (16.96%)<br>31 | 20 / 111 (18.02%)<br>32 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 7 / 114 (6.14%)<br>7    | 2 / 112 (1.79%)<br>3    | 6 / 111 (5.41%)<br>6    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 10 / 114 (8.77%)<br>16  | 2 / 112 (1.79%)<br>3    | 15 / 111 (13.51%)<br>18 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 18 / 114 (15.79%)<br>19 | 30 / 112 (26.79%)<br>54 | 11 / 111 (9.91%)<br>13  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 6 / 114 (5.26%)<br>8    | 18 / 112 (16.07%)<br>29 | 8 / 111 (7.21%)<br>9    |
| Psychiatric disorders  |                         |                         |                         |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)              | 9 / 114 (7.89%)<br>16   | 7 / 112 (6.25%)<br>18   | 8 / 111 (7.21%)<br>15   |
| Insomnia   |                         |                         |                         |

|                                    |                   |                   |                   |
|------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed        | 13 / 114 (11.40%) | 8 / 112 (7.14%)   | 7 / 111 (6.31%)   |
| occurrences (all)                  | 21                | 10                | 7                 |
| Nervousness                        |                   |                   |                   |
| subjects affected / exposed        | 6 / 114 (5.26%)   | 6 / 112 (5.36%)   | 6 / 111 (5.41%)   |
| occurrences (all)                  | 7                 | 6                 | 7                 |
| Infections and infestations        |                   |                   |                   |
| Nasopharyngitis                    |                   |                   |                   |
| subjects affected / exposed        | 6 / 114 (5.26%)   | 3 / 112 (2.68%)   | 6 / 111 (5.41%)   |
| occurrences (all)                  | 7                 | 3                 | 7                 |
| Metabolism and nutrition disorders |                   |                   |                   |
| Decreased appetite                 |                   |                   |                   |
| subjects affected / exposed        | 15 / 114 (13.16%) | 31 / 112 (27.68%) | 12 / 111 (10.81%) |
| occurrences (all)                  | 20                | 44                | 23                |
| Increased appetite                 |                   |                   |                   |
| subjects affected / exposed        | 12 / 114 (10.53%) | 4 / 112 (3.57%)   | 9 / 111 (8.11%)   |
| occurrences (all)                  | 15                | 4                 | 11                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 08 February 2011 | <p>The following changes to study inclusion criteria and procedures were made based on communications with country-specific Ethics Committees:</p> <ul style="list-style-type: none"><li>*Following responses from the Ethics Committees in Spain, Germany, and The Netherlands, an Exclusion Criterion (#2) was added: "Subject is well-controlled on their current ADHD medication, with acceptable tolerability and the parent/caregiver does not object to the current medication."</li><li>*Following a request from the French Ethics Committee, all CYP2D6 inhibitors were prohibited from use during the study, without exception and Exclusion Criterion (#10) that details use of prohibited medications was modified to include CYP2D6 inhibitors. In addition, the washout schedule for CYP2D6 inhibitors was modified such that all CYP2D6 inhibitors were required to have a 30-day washout period prior to the Baseline Visit (Visit 2/Week 0). Additional text was inserted as a prompt that these medications may have signaled the presence of an exclusionary diagnosis (Exclusion Criterion #10).</li></ul> <p>Other changes included:</p> <ul style="list-style-type: none"><li>*Neutrophil band analysis was removed.</li><li>*Screening for methylphenidate was removed from drug and alcohol screen.</li><li>* Appendix 2.5 presenting stature-for-age percentiles was inserted.</li></ul> |
| 15 February 2012 | <p>In the context of the challenges with recruitment and enrollment in the study, the statistical power of the study was decreased to 80% and the numbers of subjects required was decreased accordingly. Approximately 333 subjects (111 per treatment arm) was changed to approximately 252 subjects (84 per treatment arm). The number of subjects assessed for the primary efficacy was decreased according to the decreased power of the study. Approximately 210 subjects (105 subjects in each of the SPD503 and placebo groups) was changed to approximately 158 subjects (79 subjects in each of the SPD503 and placebo groups).</p>  |
| 24 July 2012     | <p>The approximate number of subjects to be randomized was increased back to the original target number (ie, 333). The increase was in response to a higher than anticipated recruitment rate. Approximately 252 subjects (84 per treatment arm) was changed to approximately 333 subjects (111 per treatment arm). The numbers of subject assessed for primary efficacy was increased as enrollment rates had improved and the statistical power of the study was increased from 80% (as per Amendment 3) to the original 90%.</p>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported