15 December 2016
EMA/CHMP/61393/2017
Human Medicines Evaluation Division

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Intuniv

guanfacine

Procedure no: EMEA/H/C/003759/P46/003.1

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# 1. Introduction

The MAH submitted a completed paediatric study in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Clinical aspects*

## *2.2. Introduction*

The MAH submitted a final report for an ongoing 2-year multi-center open-label extension study of guanfacine 1-7mg in children and adolescents who were diagnosed with ADHD and had participated in two preceding placebo-controlled studies, one short term study among 6-17 year olds and one randomised-withdrawal study. Objectives were to evaluate the long-term safety and tolerability of guanfacine, to provide access to guanfacine following participation in the preceding studies, and to assess maintenance of efficacy.

## *2.3. Clinical study*

### Methods

#### *Study population /Sample size*

The study was conducted at 52 sites in 11 countries in Europe: Austria, Belgium, France, Germany, Italy, The Netherlands, Poland, Romania, Spain, Ukraine, and United Kingdom. Approximately 249 patients were expected to be eligible to be enrolled in this study. In total, 218 patients were screened for participation.

#### *Treatments*

Patients were treated using guanfacine extended release 1-7mg for a 7-week dose optimization period, a 95-week dose maintenance period, and a 2-week dose taper period.

#### *Outcomes/endpoints*

Efficacy was assessed using the ADHD Rating Scale-IV (ADHD-RS-IV) and the Clinical Global Impressions - Severity of Illness (CGI-S) scale.

Safety was assessed including treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), clinical laboratory assessments, physical examination assessments

(including height, weight, and BMI assessments), and the Columbia-Suicide Severity Rating Scale (C-SSRS).

## Results

### *Recruitment / Number analysed*

A total of 215 patients were enrolled, of whom 133 subjects (62.1%) completed the study. The mean (SD) length of exposure to guanfacine was 564.5 (238.08) days with a median duration of exposure of 708 days. Disposition of patients see table 1 below:

| | 6-12 Years N=131 n (%) | 13-18 Years N=84 n (%) | Total N=215 n (%) |
|---|---|---|---|
| Screened subjects | 132 | 86 | 218 |
| Enrolled subjects | 131 | 84 | 215 |
| Safety analysis set[a] | 131 (100) | 83 (98.8) | 214 (99.5) |
| Full analysis set[b] | 128 (97.7) | 81 (97.6) | 209 (97.7) |
| Completed study | 79 (60.3) | 54 (65.1) | 133 (62.1) |
| Did not complete study | 52 (39.7) | 29 (34.9) | 81 (37.9) |
| Primary reason for withdrawal | | | |
| Adverse event | 4 (3.1) | 3 (3.6) | 7 (3.3) |
| Protocol violation | 0 | 1 (1.2) | 1 (0.5) |
| Withdrawal by subject | 23 (17.6) | 14 (16.9) | 37 (17.3) |
| Lost to follow-up | 2 (1.5) | 3 (3.6) | 5 (2.3) |
| Lack of efficacy | 14 (10.7) | 5 (6.0) | 19 (8.9) |
| Other | 9 (6.9) | 3 (3.6) | 12 (5.6) |
| Antecedent study SPD503-315 (randomized treatment) | 50 (38.2) | 26 (31.3) | 76 (35.5) |
| SPD503 | 29 (22.1) | 14 (16.9) | 43 (20.1) |
| Placebo | 21 (16.0) | 12 (14.5) | 33 (15.4) |
| Antecedent study SPD503-316 (randomized treatment) | 81 (61.8) | 57 (68.7) | 138 (64.5) |
| SPD503 | 22 (16.8) | 23 (27.7) | 45 (21.0) |
| STRATTERA | 36 (27.5) | 12 (14.5) | 48 (22.4) |
| Placebo | 23 (17.6) | 22 (26.5) | 45 (21.0) |

[a] The safety analysis set included all subjects who received at least 1 dose of SPD503. Percentages for the safety analysis set were based on enrolled subjects in that age group. Other percentages were based on the safety analysis set for that age group.

[b] The full analysis set included all subjects who received at least 1 dose of SPD503 except for subjects from Site 403.

**Table 1 Disposition of patients**

### *Baseline data*

At baseline, the overall mean (SEM) ADHD-RS-IV total score was 36.6 (0.73); mean (SEM) subscale scores were 17.2 (0.45) for hyperactivity/impulsivity and 19.4 (0.36) for inattentiveness. At baseline, 2 patients (1%), both aged 13-18 years, were considered to show normal/borderline illness severity on the CGI. The remaining 206 patients were considered mildly affected or greater.

***Efficacy results***

At the final 95-week assessment, the overall mean (SEM) change in ADHD-RS-IV total score from baseline was -19.8 (0.84); mean (SEM) changes in subscale score were -10.1 (0.44) for hyperactivity/impulsivity and -9.8 (0.47) for inattentiveness.

At the final assessment, 96 patients (46.4%) were categorized as CGI normal/borderline severity including 45 (35.4%) of all patients aged 6-12 years and 51 (63.8%) of all patients aged 13-18 years.

CHMP comment:

A considerably larger proportion of adolescents shifted in CGI-category when compared with the data submitted as part of the original MAA. The MAH is requested to discuss this difference.

***Safety results***

Overall, 82.7% of all patients experienced TEAE's (6-12year olds: 84.7%; 13-17 year olds: 79.5%). The most frequently reported were somnolence, headache, fatigue, nasopharyngitis, dizziness, insomnia, nausea, abdominal pain, vomiting, and rhinitis, oropharyngeal pain and upper respiratory tract infection, see table 2.

| | 6-12 Years N=131 | | 13-18 Years N=83 | | Total N=214 | |
|---|---|---|---|---|---|---|
| **Preferred Term** | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** |
| Somnolence | 50 (38.2) | 82 | 27 (32.5) | 37 | 77 (36.0) | 119 |
| Headache | 38 (29.0) | 91 | 23 (27.7) | 43 | 61 (28.5) | 134 |
| Fatigue | 30 (22.9) | 43 | 13 (15.7) | 15 | 43 (20.1) | 58 |
| Nasopharyngitis | 7 (5.3) | 14 | 18 (21.7) | 24 | 25 (11.7) | 38 |
| Dizziness | 12 (9.2) | 16 | 9 (10.8) | 10 | 21 (9.8) | 26 |
| Insomnia | 10 (7.6) | 10 | 6 (7.2) | 7 | 16 (7.5) | 17 |
| Nausea | 12 (9.2) | 15 | 2 (2.4) | 2 | 14 (6.5) | 17 |
| Upper respiratory tract infection | 9 (6.9) | 16 | 4 (4.8) | 10 | 13 (6.1) | 26 |
| Abdominal pain | 9 (6.9) | 11 | 4 (4.8) | 4 | 13 (6.1) | 15 |
| Vomiting | 8 (6.1) | 12 | 3 (3.6) | 4 | 11 (5.1) | 16 |
| Rhinitis | 8 (6.1) | 11 | 3 (3.6) | 3 | 11 (5.1) | 14 |
| Oropharyngeal pain | 7 (5.3) | 8 | 4 (4.8) | 5 | 11 (5.1) | 13 |
| Abdominal pain upper | 8 (6.1) | 11 | 2 (2.4) | 2 | 10 (4.7) | 13 |
| Diarrhoea | 7 (5.3) | 8 | 3 (3.6) | 3 | 10 (4.7) | 11 |
| Pyrexia | 8 (6.1) | 9 | 2 (2.4) | 2 | 10 (4.7) | 11 |
| Aggression | 7 (5.3) | 7 | 2 (2.4) | 3 | 9 (4.2) | 10 |

m=number of events; n=number of subjects reporting the event.

Note: Adverse events were classified into preferred term using Version 12.1 of the Medical Dictionary for Regulatory Activities. Subjects were counted once per preferred term.

**Table 2: Treatment-emergent Adverse Events Occurring in at Least 5%**

No deaths occurred during the study.

Ten patients had serious TEAEs. These included (classified as): appendicitis (severe), gastroenteritis (severe), stomatitis (moderate), lower limb fracture (moderate), concussion (1 moderate; 1 mild), radius fracture (severe), upper limb fracture (mild), wrist fracture (severe), testicular torsion (moderate), postprocedural hemorrhage (moderate) and aggression (moderate).

Overall, 26.6% of all patients experienced a TEAE that required dose reduction (6-12year olds: 31.3%; 13-17 year olds: 19.3%). Seven patients discontinued treatment due to TEAE's (6-12year olds: 3.1%; 13-17 year olds: 3.6%). These included weight increase, dizziness, somnolence (2 patients), atrioventricular block, drug abuse, and aggression.

No new safety signals were identified in terms of TEAE incidence, severity, or specificity; clinical laboratory assessments; vital signs; ECG; and C-SSRS. No new cases of QT-interval prolongation or bradycardia were identified.

Sedative events were reported in 51 patients (38.9%) aged 6-12 years and in 30 patients (36.1%) aged 13-18 years. The mean (SD) duration of sedation was 33.4 (62.21) days in 6-12 year olds and 76.2 (138.99) days in 13-18 year olds. The incidence was highest in the first few weeks of treatment (see figure 1):

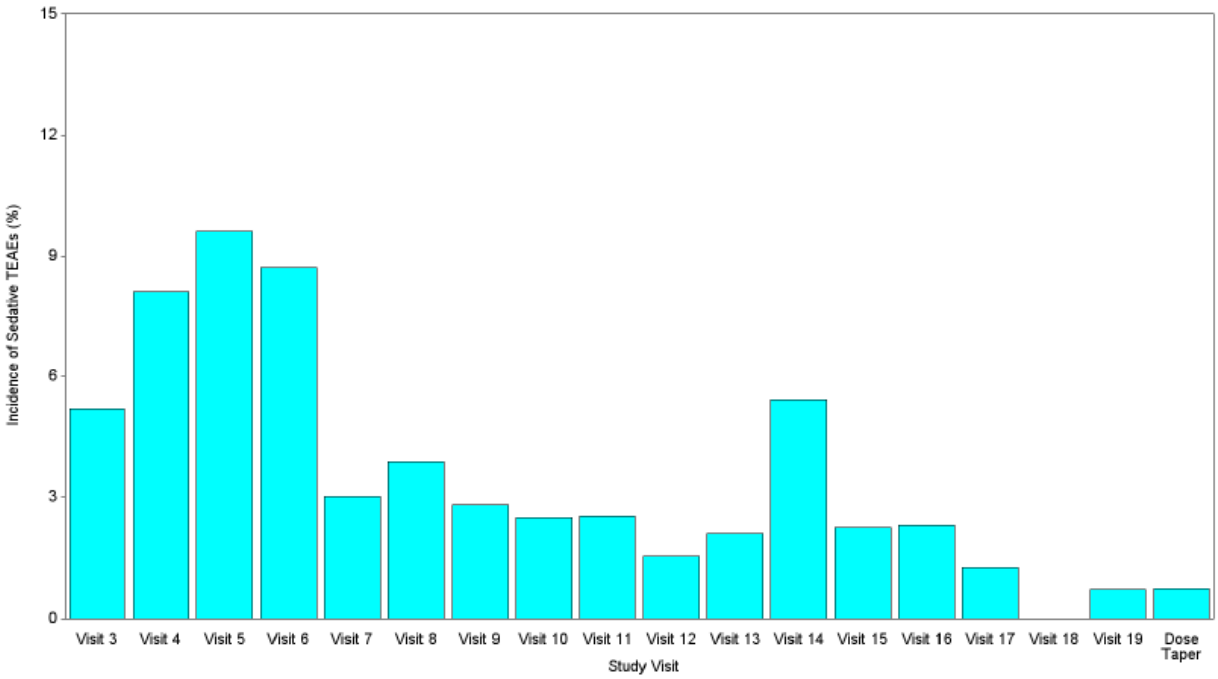



**Figure 1: Incidence of Treatment-emergent Sedative Adverse Events**

At the final study assessment, 25 patients (11.7% of the safety analysis set) had a shift in BMI from healthy BMI (⩾5th percentile and <85th percentile) at baseline to overweight (⩾85th percentile and <95th percentile) or obese (⩾95$^{th}$ percentile), or a shift from overweight at baseline to obese.

CHMP comment:

The clinical relevance of BMI percentile-shifts is considered difficult to assess. The MAH is requested to submit proportions of patients (children and adolescents separately) with a clinically relevant increase in BMI-increase at final assessment as compared to baseline.

## 3. CHMP's overall conclusion and recommendation

Given the open-label study design, no firm conclusions can be drawn regarding maintenance of efficacy. It is, however, noted, that this was less favourable for youngest age group (6-12 y old) versus older children and adolescents.

The B/R balances remains positive. No essential new adverse events emerged, although it seems that overweight/obesity incidence increases at longer follow-up, given the lower incidences that were reported before in the SmPC. Overall drop-out due to AEs was low and similar between age groups, hence the B/R remains positive.

## 4. Assessment of response

1. A considerably larger proportion of adolescents shifted in CGI-category when compared with the data submitted as part of the original MAA. The MAH is requested to discuss this difference between age groups.

**MAH response**

To clarify, because the CGI-S was used in study SPD503-318 and not the CGI-I that had been used in other clinical studies, a direct comparison of results between the different questionnaires cannot be made. Both scales are scored on a Likert scale from 1 to 7; however, the CGI-S describes the severity of illness and the CGI-I describes improvement since a specified time.

| CGI scale: | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| CGI-S: | not assessed | normal, not at all ill | borderline ill | mildly ill | moderately ill | markedly ill | severely ill | among the most extemely ill subjects |
| CGI-I: | not assessed | very much improved | much improved | minimally improved | no change | minimally worse | much worse | very much worse |

A summary of CGI-S scores by age-group at baseline, week 12, and at the final assessment of studies SPD503-318 and SPD503-315 are provided in Table 1 and Table 2, respectively. Because study SPD503-318 is a rollover study of studies SPD503-315 and SPD503-316, an understanding of CGI-S scores by age group in the precedent studies is helpful to explain distribution of scores by age group in the rollover study. The CGI-S scores at week 12 are included in the presentation of SPD503-318 results to allow for comparisons with the CGI-S score endpoint at the end of the open-label period of the SPD503-315 study.

**Table 1. Number (Percentage) of Subjects and CGI-S scores in the Open-Label Roll-Over Study SPD503-318 (Full Analysis Set)**

| | N (%) 6 to 12 year olds N=128 | | | N (%) 13 to 17 year olds N=81 | | |
|---|---|---|---|---|---|---|
| CGI-S score | Baseline | Week 12 | Final Assessment | Baseline | Week 12 | Final Assessment |
| 1 normal, not at all ill | 0 | 12 (10.1) | 18 (14.2) | 0 | 11 (14.7) | 22 (27.5) |
| 2 borderline ill | 0 | 36 (30.3) | 27 (21.3) | 2 (2.5) | 35 (46.7) | 29 (36.3) |
| 3 mildly ill | 6 (4.7) | 40 (33.6) | 39 (30.7) | 18 (22.2) | 21 (28.0) | 19 (23.8) |
| 4 moderately ill | 27 (21.3) | 22 (18.5) | 24 (18.9) | 29 (35.8) | 5 (6.7) | 6 (7.5) |
| 5 markedly ill | 51 (40.2) | 8 (6.7) | 13 (10.2) | 22 (27.2) | 3 (4.0) | 3 (3.8) |
| 6 severely ill | 40 (31.5) | 1 (0.8) | 5 (3.9) | 8 (9.9) | 0 | 1 (1.3) |
| 7 among the most extemely ill | 3 (2.4) | 0 | 1 (0.8) | 2 (2.5) | | 0 |

Source: SPD503-318 CSR Table 3.2.5

The distribution pattern among the CGI-S scores is similar between the 2 age groups and as seen in the antecedent study SPD503-315. At baseline, the subjects in study SPD503-318 were less ill than subjects in the SPD503-315 study, which is not surprising considering that most subjects had had received treatment for ADHD symptoms in the antecedent studies SPD503-315 and SPD503-316 (SPD503ANT). At week 12, 40 subjects aged 6 to 12 years subjects (33.6%) and 21 subjects aged 13 to 17 years (28.0%) were considered mildly ill; 36 subjects aged 6 to 12 years (30.3%) and 35 subjects aged 13 to 17 years (46.7%) were considered borderline ill. At the final assessment, a greater proportion of the adolescent subjects had a CGI-S score of 1 or 2 and were considered either normal or borderline ill. In contrast, a greater proportion of the children had a CGI-S score of either 2 or 3.

A presentation of CGI-S scores by age-group at the start and the end of the SPD503 dose optimization period of study SPD503-315 is provided in Table 2. At baseline, all subjects were at least moderately ill and nearly half of subjects in both age groups were considered to be markedly ill (47.9% of subjects aged 6 to 12 years and 53.5% of subjects aged 13 to 17 years. At the the final assessment LOCF (visit 13/week 13), the distribution of milder category scores was proportional between the 2 age subgroups: the greatest proportion of

subjects shifted to the borderline ill category (186 subjects aged 6 to 12 years [49.9%] and 52 subjects [41.6%]; which was followed with a shift to the normal, not at all ill category (71 subjects aged 6 to 12 years [19.0%] and 34 subjects aged 13 to 17 years [27.2%].

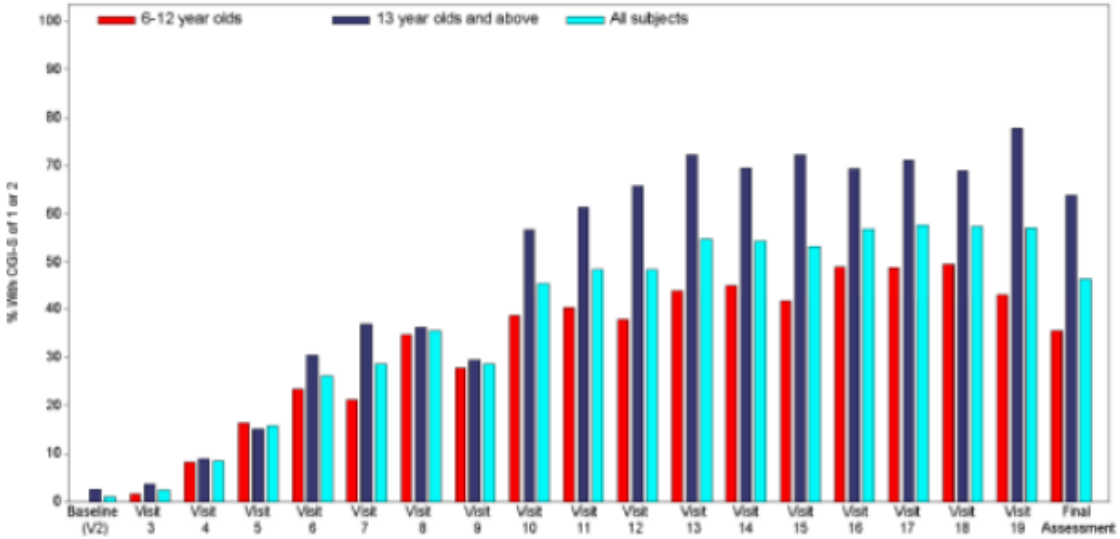
**Table 2. Number (Percentage) of Subjects and CGI-S Scores during the Open-Label Period of Study SPD503-315 (Full Analysis Set)**

| | 6 to 12 year olds N=376 | | 13 to 17 year olds N=127 | |
|---|---|---|---|---|
| CGI-S score | Baseline | Endpoint[a] | Baseline | Endpoint[a] |
| 1 normal, not at all ill | 0 | 71 (19.0) | 0 | 34 (27.2) |
| 2 borderline ill | 0 | 186 (49.9) | 0 | 52 (41.6) |
| 3 mildly ill | 0 | 29 (7.8) | 0 | 17 (13.6) |
| 4 moderately ill | 70 (18.6) | 54 (14.5) | 41 (32.3) | 14 (11.2) |
| 5 markedly ill | 180 (47.9) | 24 (6.4) | 68 (53.5) | 8 (6.4) |
| 6 severely ill | 104 (27.7) | 9 (2.4) | 14 (11.0) | 0 |
| 7 among the most extemely ill | 22 (5.9) | 0 | 4 (3.1) | 0 |

a Endpoint is the final assessment and equivalent to week 13 (visit 13) using LOCF.
Source: SPD503-315 CSR Table 3.2.5.2

As shown in Figure 1, a greater proportion of adolescents had milder CGI-S scores compared with children in the roll-over study SPD503-318.

**Figure 1. Proportion of Subjects with CGI-S Score of 1 (Normal) or 2 (Borderline) by Visit and Age Group in the Roll-Over Study SPD503-318 (Full Analysis Set)**



Source: SPD503-318 CSR Figure 3.2.5

Several factors differentiate study SPD503-318 from the phase 3 studies that comprised the MAA. Firstly, the subjects enrolled in SPD503-318 had been enrolled in the antecedent studies (SPD503ANT) SPD503-315 or SPD503-316. In both antecedent studies, a minimum baseline CGI-S score of 4 was necessary for inclusion. This criterion could not be adopted in the SPD503-318 study because most of the subjects who participated in this safety extension study had had prior exposure to either SPD503 (from SPD503-316 or from the open-label

period of SPD503-315) or atomoxetine (from SPD503-316). Also, the adolescent subjects in the SPD503-318 study could have been some of the children in the antecedent studies. It is well-known, that adolescent responses vary relative to children for many reasons including general engagement (Field 2004). Rebellion against adult authority, peer pressure, and inadequate time for training and preparation of the adolescent subject are also known behavioral confounders in clinical studies with adolescents. Consistent with this, CGI-S scores in the short-term SPD503 studies have not shown as robust improvement as has been observed in the SPD503-318 longer-term rollover study, presumably because these subjects who were enrolled in a prior clinical studies with SPD503 are better prepared and more engaged with the experience of and having had made connections with study staff in one of precedent studies to this extension study.

| |
|---|
| CHMP comment:<br>The MAH response is considered acceptable. The difference may be consistent with the selection of treatment-responsive subjects in the preceding studies by differential discontinuations /drop-outs. In addition, no firm conclusions can be drawn regarding efficacy from this study, given the open-label and uncontrolled study design.<br>Issue resolved. |

2. One additional issue that may need additional analysis is the difference between subjects aged 6-12 years and subjects aged 13-18 years in regard to discontinuation of treatment due to lack of efficacy: 10.7% vs. 6.0%.

**MAH response**

Although SPD503-318 was not designed to be an efficacy study, maintenance of response was observed after 2 years of treatment with SPD503 in addition to the efficacy achieved in the antecedent studies SPD503-315 and SPD503-316, which each had 13-week treatment periods. SPD503 was effective compared to placebo in the treatment of ADHD symptoms in studies SPD503-315 and SPD503-316.

A total of 209 subjects (97.7%) comprised the full analysis set of the SPD503-318 study. Of these 209 subjects, 128 subjects (61.2%) were aged 6 to 12 years and 81 subjects (38.8%) were aged 13 to 17 years. The study was completed by 61.7% and 66.7% of subjects in the 6 to 12 year and the 13 to 17 year age subgroups, respectively, in the full analysis set.

Of the subjects who transitioned from the SPD503-315 study, subject random assignments

were as follows:

- 43 subjects assigned to SPD503
    - 29 subjects aged 6 to 12 years
    - 14 subjects aged 13 to 17 years
- 33 subjects assigned to placebo
    - 21 subjects aged 6 to 12 years
    - 12 subjects aged 13 to 17 years

Of the subjects who transitioned from the SPD503-316 study, subject random assignments were as follows:

- 45 subjects assigned to SPD503
    - 22 subjects aged 6 to 12 years
    - 23 subjects aged 13 to 17 years
- 45 subjects assigned to placebo
    - 23 subjects aged 6 to 12 years
    - 22 subjects aged 13 to 17 years
- 48 subjects assigned to atomoxetine
    - 36 subjects aged 6 to 12 years
    - 12 subjects aged 13 to 17 years

Shown in Table 3, at study SPD503-318 baseline, the overall mean (SEM) ADHD-RS-IV total score was 36.6 (0.73). Overall, the younger subgroup had worse ADHD-RS-IV total scores: mean (SEM) total scores for the 2 age groups were 40.0 (0.78) in subjects aged 6 to 12 years and 31.2 (1.19) years in subjects aged 13 to 17 years.

The overall mean (SEM) change from baseline in SPD503-318 in ADHD RS-IV total score was -20.2 (0.75) after 6 months, -21.5 (0.81) after 12 months, and -22.7 (0.86) after 18 months. Small differences in the changes from baseline at 6, 12, or 18 months were observed between subjects aged 6 to 12 years and those aged 13 to 17 years: 21.0 (0.98) compared with -19.0 (1.17) at 6 months; 22.3 (1.08) compared with -20.2 (1.19) at 12 months; and 23.8 (1.13) compared with 21.0 (1.30) at 18 months.

**Table 3. Observed Values and Changes from Baseline318 in the ADHD-RS-IV Total Score by Age Group (Full Analysis Set)**

| | 6 to 12 Years N=128 | 13-17 Years N=81 | Total N=209 |
|---|---|---|---|
| **$Baseline_{318}$** | | | |
| n | 127 | 81 | 208 |
| Mean (SEM) | 40.0 (0.78) | 31.2 (1.19) | 36.6 (0.73) |
| Median | 42.0 | 31.0 | 39.0 |
| Min, max | 13, 54 | 4, 54 | 4, 54 |
| **Visit 13 (Day 196/Month 6) - observed value** | | | |
| n | 116 | 72 | 188 |
| Mean (SEM) | 18.8 (0.93) | 12.1 (0.86) | 16.2 (0.70) |
| Median | 17.0 | 11.0 | 14.0 |
| Min, max | 0, 46 | 0, 36 | 0, 46 |
| **Visit 13 (Day 196/Month 6) - change from $baseline_{318}$** | | | |
| n | 115 | 72 | 187 |
| Mean (SEM) | -21.0 (0.98) | -19.0 (1.17) | -20.2 (0.75) |
| Median | -20.0 | -17.5 | -19.0 |
| Min, max | -48, 4 | -48, 7 | -48, 7 |
| **Visit 15 (Day 364/Month 12) - observed value** | | | |
| n | 108 | 65 | 173 |
| Mean (SEM) | 17.1 (0.93) | 10.8 (0.79) | 14.7 (0.69) |
| Median | 16.0 | 10.0 | 12.0 |
| Min, max | 1, 45 | 0, 29 | 0, 45 |
| **Visit 15 (Day 364/Month 12) - change from $baseline_{318}$** | | | |
| n | 107 | 65 | 172 |
| Mean (SEM) | -22.3 (1.08) | -20.2 (1.19) | -21.5 (0.81) |
| Median | -21.0 | -19.0 | -21.0 |
| Min, max | -47, 7 | -48, 1 | -48, 7 |
| **Visit 17 (Day 532/Month 18) - observed value** | | | |
| n | 92 | 59 | 151 |
| Mean (SEM) | 15.6 (0.97) | 9.3 (0.70) | 13.1 (0.70) |
| Median | 13.0 | 9.0 | 12.0 |
| Min, max | 0, 41 | 0, 23 | 0, 41 |
| **Visit 17 (Day 532/Month 18) - change from $baseline_{318}$** | | | |
| n | 91 | 59 | 150 |
| Mean (SEM) | -23.8 (1.13) | -21.0 (1.30) | -22.7 (0.86) |
| Median | -22.0 | -20.0 | -21.0 |
| Min, max | -48, 1 | -48, 2 | -48, 2 |

| | 6 to 12 Years N=128 | 13-17 Years N=81 | Total N=209 |
|---|---|---|---|
| **Final assessment - observed value** | | | |
| n | 127 | 80 | 207 |
| Mean (SEM) | 19.8 (1.13) | 12.0 (1.07) | 16.8 (0.85) |
| Median | 18.0 | 10.0 | 14.0 |
| Min, max | 0, 50 | 0, 54 | 0, 54 |
| **Final assessment - change from baseline$_{318}$** | | | |
| n | 126 | 80 | 206 |
| Mean (SEM) | -20.2 (1.10) | -19.3 (1.31) | -19.8 (0.84) |
| Median | -19.5 | -19.0 | -19.0 |
| Min, max | -47, 11 | -48, 14 | -48, 14 |
| p-value[a] | <0.0001 | <0.0001 | <0.0001 |

ADHD-RS-IV=Attention-deficit/Hyperactivity Disorder Rating Scale IV; baseline$_{318}$=baseline of study SPD503-318; max=maximum; min=minimum; SEM=standard error of the mean.

Note: The ADHD-RS-IV total score spans 0 (no symptoms) to 54 (most severe symptoms). Final assessment was the last valid assessment obtained after baseline (visit 2) while on SPD503 and before the first tapered dose of medication.

a Nominal p-value, with no adjustment for multiple testing, from a 1-sample *t*-test assessing whether the change from baseline (visit 2) to final assessment equals zero.

Source: SPD503-318 CSR Section 14, Table 3.2.1.1.2

The primary reason for study withdrawal was lack of efficacy in 14 subjects aged 6 to 12 years and 5 subjects aged 13 to 17 years. Demographics and ADHD-RS-IV scores are provided for these subjects in Table 4. All of the subjects in Table 4 reported race of white and have an ADHD combined subtype diagnosis; except for Subject 604-0001 who has predominantly inattentive subtype.

**Table 4. Subjects with "Lack of efficacy" Given as the Primary Reason for Discontinuation of Study SPD503-318**

| Subject No. | sex/age | SPD503 exposure (days)/Exit visit | Years since | | Prior pschoactive medications | ADHD-RS-IV total score (0 to 54) | | |
|---|---|---|---|---|---|---|---|---|
| | | | symptom onset | ADHD diagnosis | | Baseline$_{ANT}$ | Baseline$_{318}$ | ≥30% reduction from baseline$_{318}$ |
| **Children aged 6 to 12 years** | | | | | | | | |
| 001-0001 | M/8 | 173/V13 | 2 | 2 | ATX | 37 | 42 | yes, visits 5, 6, and 10 |
| 052-0002 | M/9 | 659/V19 | 6 | 4 | MPH | 51 | 39 | yes, visits 6, 7, 10, 14–17 |
| 258-0002 | M/12 | 373/V16 | 5 | 5 | none | 44 | 40 | yes, visits 4-16 |
| 264-0001 | M/9 | 490/V17 | 2 | 1 | MPH AMP resperidone | 43 | 45 | yes, visits 3-12, 14-16 |
| 354-0005 | M/11 | 447/V16 | 8 | 1 | none | 45 | 49 | yes, visits 10, 11 |
| 357-0002 | M/11 | 435/V16 | 9 | 3 | none | 45 | 25 | yes, visits 5-12 |

| Subject No. | sex/age | SPD503 exposure (days)/Exit visit | Years since | | Prior pschoactive medications | ADHD-RS-IV total score (0 to 54) | | |
|---|---|---|---|---|---|---|---|---|
| | | | symptom onset | ADHD diagnosis | | $Baseline_{ANT}$ | $Baseline_{318}$ | ≥30% reduction from $baseline_{318}$ |
| **Children aged 6 to 12 years** | | | | | | | | |
| 360-0001 | M/12 | 588/V18 | 7 | 3 | MPH resperidone | 45 | 20 | yes, visits 3-14 |
| 502-0001 | M/11 | 280/V14 | NA | 3 | ATX MPH | 45 | 37 | yes, visits 11, 12 |
| 604-0002 | F/11 | 48/V8 | 6 | 6 | MPH | 51 | 51 | no |
| 701-0004[a] | M/10 | 475/V17 | 2 | 1 | ATX MPH | 54 | 53 | yes, visits 3-17 |
| 702-0002 | M/12 | 672/V19 | 11 | 5 | none | 53 | 53 | yes, visits 8-19 |
| 706-0002 | F/10 | 676/V19 | 8 | 1 | ATX | 45 | 39 | yes, visits 9, 12-17, 19 |
| 706-0003 | M/7 | 378/V15 | 5 | 0 | none | 49 | 45 | yes, visits 4-12, 14 |
| 710-0002 | M/8 | 37/V6 | 1 | 0 | none | 53 | 48 | no |
| **Adolescents aged 13 to 17 years** | | | | | | | | |
| 266-0017 | M/14 | 434/V16 | 8 | 1 | MPH | 45 | 35 | yes, visits 10-16 |
| 505-0002 | M/18 | 107/V11 | 4 | 4 | MPH | 38 | 36 | yes, visits 6, 8, 10 |
| 604-0001[b] | F/14 | 35/V7 | 7 | 1 | MPH | 44 | 39 | no |
| 607-0003 | F/17 | 22//V6 | 12 | 0 | none | 37 | 24 | no |
| 702-0001[a] | F/13 | 238/V14 | 6 | 4 | ATX MPH | 52 | 54 | yes, visit 13 |

Source: Listings 1.3, 4.3, 4.4, 4.6, 6.3

Abbreviations: ADHD-RS-IV=Attetion-deficit/hyperactivity disorder-ratiting scale IV; AMP=amphetamine; ATX=atomoxetine; $Baseline_{ANT}$=value at the baseline of the antecedent study, SPD503-315 or 316; F=female; M=male; NA=not available; V=visit

a Subject has current comorbidity of oppostional defiant disorder

b All subjects in this table are diagnosed with the ADHD combined subtype except for Subject 604-001 who has been diagnosed with the predominantly inattentive subtype.

All patients from the SPD503-315 study had had experience with SPD503 treatment during the open-label lead-in period. In contrast, approximately 2/3 of subjects from the SPD503-316 study did not. Accordingly, all subjects in the SPD503-315 study had ample opportunity drop out of the study due to lack of efficacy before being rolled over into the extension SPD503-318 study, while 2/3 of subjects in the SPD503-316 study did not. Furthermore, the subjects who discontinued due to lack of efficacy had some of the most severe ADHD-RS-IV total scores at the baselines of the antecedent studies and of the SPD503-318 study. No prior treatment with any psychoactive medication was reported in 6 of the subjects aged 6 to 12 years. Oppositional defiant disorder was a co-morbidity in 2 subjects who withdrew due to lack of efficacy: 1 subject from each age group. The majority of subjects who withdrew due

to reported lack of efficacy had ⩾30% reduction in baseline318 ADHD-RS-IV total score at several study visits, which would be a greater reduction in ADHD symptoms than that observed at the baseline of the antecedent studies (baseline ANT).

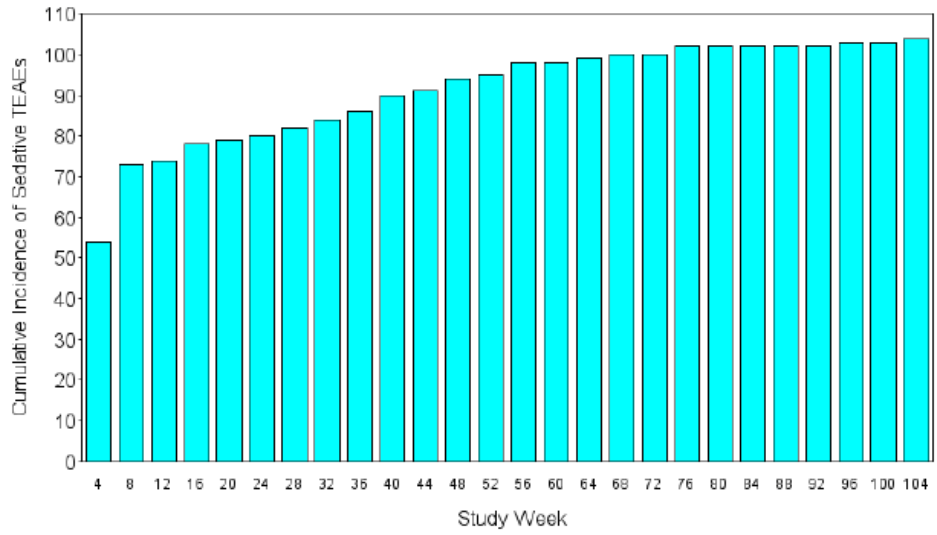
| CHMP comment: |
| --- |
| The MAH response is considered acceptable. The study enrolled a selection of –to some extent- more guanfacine-responsive subjects in particular in the older age-group from the preceding trials. Issue resolved. |

3. Regarding sedative TEAE's, the cumulative incidence by treatment week should be analysed throughout study duration

**MAH response**

In the SPD503-318 clinical study, subjective-sedative-related effects were examined through spontaneously reported sedative AEs (somnolence, sedation, and hypersomnia). The cumulative incidence of sedative TEAEs by study week is presented in Figure 2.

**Figure 2. Cumulative Incidences of Sedative TEAEs by Study Week During Study SPD503-318**




Program Path: /sp/spd503/study318/dev/work/adhoc/programs/r2329_f_ae.sas

Note: Sedative TEAEs included somnolence, sedation, and hypersomnia.

Sedative events were reported in 51 subjects (38.9%) aged 6 to 12 years and 30 subjects (36.1%) aged 13 to 17 years. The mean (SD) number of treatment-emergent sedative events per subject was 1.6 (1.02) in subjects aged 6 to 12 years and 1.4 (0.89) in subjects aged 13 to 17 years. The mean (SD) duration of individual events was 33.4 (62.21) days for subjects aged 6 to 12 years and 76.2 (138.99) days for subjects aged 13 to 17 years.

As observed in prior studies, incidence of sedative events is greatest during the early study

weeks. Reports decline as the study progresses, as observed in the flatter slope in Figure 2 in later study weeks. Sedative events were generally self-limiting, with the majority of treatment-emergent sedative adverse events resolving before the start of the dose taper period: 94.0% of events in subjects aged 6 to 12 years and 80.5% of subjects aged 13 to 17 years. The majority of sedative events (118 of 125 events; 94.4%) were mild or moderate. Three subjects (5.9%) aged 6 to 12 years and 4 subjects (13.3%) aged 13-18 years had a worst TEAE severity of severe. Two events (2.4%; both somnolence) in subjects aged 6 to 12 years led to discontinuation ( "drug withdrawn" ). Twenty-one sedative TEAEs (25.0%; all somnolence) in subjects aged 6 to 12 years and 10 sedative TEAEs (24.4%; 9 somnolence and 1 hypersomnia) in subjects aged 13 to 17 years resulted in a dose reduction.

CHMP comment:

The MAH response is considered acceptable. The sedation profile in the results of the submitted study is in accordance with the issue identified in the MAA and represented in the product information. This issue has been appropriately addressed in the SmPC, where continuous monitoring regarding somnolence throughout treatment is advised.

Issue solved.

4. In the current SmPC, serious weight increase is only reported in 2.9% of the cases. Not unexpectedly, the incidence of BMI shifts to overweight/obesity was more common (11.7%) at longer-term follow-up. The clinical relevance of BMI percentile-shifts is considered difficult to assess. The MAH is requested to submit proportions of patients (children and adolescents separately) with a clinically relevant increase in BMI at final assessment as compared to baseline.

**MAH response**

The incidence of BMI shifts from healthy to overweight/obese was reported incorrectly as being 11.7% of subjects (25 of 214 subjects) in the original SPD503-318 clinical study report: the correct incidence of BMI shifts from healthy to overweight/obese is 7.0% (15 of 214 subjects).

At the final study assessment, 15 subjects (7.0% of the safety analysis set) had a shift from healthy BMI (≥5th percentile and <85th percentile) at baseline to overweight (≥85th percentile and <95th percentile) or obese (≥95th percentile), or a shift from overweight at baseline to obese. Of these 15 subjects, 14 subjects shifted to an overweight BMI; one subject had an

obese BMI at the final assessment. All of these subjects had a BMI percentile greater than 50% at baseline, and all of the subjects who had a shift to obese had a BMI percentile greater than 80% at baseline.

Overall, 5 subjects (2.3%) of the safety analysis set of study SPD503-318 reported 5 treatment-emergent adverse events (TEAEs) of weight increased (preferred term). All 5 subjects were between 6 and 12 years of age.

Details on these subjects with an upward shift in BMI category was reported from baseline318 to 6, 12, 18, and/or the final assessment at 24 months or early termination (ET) and for whom a report of a TEAE related to weight increase are provided in the following paragraphs. Shifts include those from healthy BMI (≥5th percentile and <85th percentile) at baseline318 to overweight BMI (≥85th percentile and <95th percentile) or obese BMI (≥95th percentile) at subsequent time points and from overweight BMI at baseline to obese BMI at subsequent time points. The BMI categories are based on the US Centers for Disease Control and Prevention Percentile Growth Charts (Please note that due to privacy laws in the EU, only the subject’s birth year can be recorded in certain regions of the EU. Consequently, growth parameters were imputed using January, June, and December birth months and some subjects who may have had BMI shifts from a healthy BMI baseline to an overweight/obese BMI at a later time point may not have had such shift when BMI was calculated using a different birth month).

Subject 001-0001 was male aged 8 years at the time of the baseline318 assessment. At baseline318, his height was 140.5 cm (99.0th percentile); his weight was 30.5 kg (86.6th percentile); and his BMI was 15.5 kg/m2 (43.2nd percentile). During the study on day 51, the subject reported a moderate TEAE of insomnia, which resulted in a dose reduction from 3 mg to 2 mg of SPD503, and the event resolved after 21 days. Also on day 51, the subject reported moderate TEAEs of abdominal pain upper and weight increased, the dose was not changed and the event resolved after 119 days. On day 100, the subject reported a mild TEAE of poor quality of sleep, the dose was not changed and the event resolved after 70 days. All of the TEAEs were considered to be related to SPD503. On day 169, the subject had an early termination visit; on day 173, the subject discontinued from the study due to lack of efficacy. At the early termination visit, he was receiving 2 mg SPD503 and his height was 142.4 cm (98.4th percentile); his weight was 37.2 kg (95.8th percentile); and his BMI was 18.3 kg/m2 (86.8th percentile). The subject previously received

atomoxetine hydrochloride for ADHD from Nov 2010 to 30 May 2012.

Subject 702-0002 was a male aged 12 years at the time of the baseline318 assessment.
At baseline318, his height, weight, and BMI were:
- 165.5 cm (94.5th percentile), 63.4 kg (95.2nd percentile), and 23.1 kg/m2
(91.7th percentile – overweight BMI), respectively
At 6 months, he was receiving 5 mg SPD503 and his height, weight, and BMI were:
- 170.5 cm (95.3rd percentile), 72.6 kg (97.5th percentile), and 25.0 kg/m2
(94.5th percentile – overweight BMI), respectively
At 12 months, he was receiving 6 mg SPD503 and his height, weight, and BMI were:
- 171.5 cm (91.7th percentile), 75.8 kg (97.6th percentile), and 25.8 kg/m2
(95.2nd percentile – obese BMI), respectively.
On day 7, while receiving 1 mg SPD503 a moderate TEAE of weight increased was reported that remained ongoing at the time of early termination. The event was considered to be related to SPD503. Other TEAEs reported included somnolence (1 mild, 1 moderate), which were considered to be related to SPD503; were moderate TEAEs of chest discomfort, aggression, hypertension, muscle spasms, and poor sleep quality, and mild TEAEs of cough, viral gastroenteritis, oropharyngeal pain, and skin striae; all of these events were considered to be not related to SPD503. On day 659, the subject was discontinued from the study due to lack of efficacy. At the early termination visit, he was receiving 6 mg SPD503 and his BMI was 29.4 kg/m2 (97.8th percentile – obese BMI). No prior use of stimulant medication was reported.

Subject 704-0001 was a male aged 8 years at the time of the baseline318 assessment.
At baseline318, his height, weight, and BMI were:
- 122.6 cm (9.1st percentile), 28.0 kg (60.1st percentile), and 18.6 kg/m2
(88.0th percentile – overweight BMI), respectively
At 6 months, he was receiving 4 mg SPD503 and his height, weight, and BMI were:
- 124.5 cm (7.7th percentile), 31.1 kg (70.5th percentile), and 20.1 kg/m2
(92.7th percentile – overweight BMI), respectively
At 12 months, he was receiving 3 mg SPD503 and his height, weight, and BMI were:
- 127.0 cm (8.6th percentile), 33.7 kg (74.9th percentile), and 20.9 kg/m2
(93.8th percentile – overweight BMI), respectively
On day 118, while receiving 4 mg SPD503, he was reported to have a mild TEAE of

decreased appetite that led to a reduction in SPD503 dose. On day 434, while receiving 3 mg SPD503, the subject was reported to have a moderate TEAE of weight increased that led to withdrawal of SPD503. Both of these events were considered to be related to SPD503. During the study, mild TEAEs of headache and terminal insomnia (2 events each) were reported, all of which were considered to be not related to SPD503. The subject was discontinued from the study on day 506 due to the AE of weight increased and had his early termination visit on the same day. At the early termination visit, his BMI was 23.9 kg/m2 (97.3rd percentile – obese BMI). No prior use of stimulant medication was reported.

Subject 052-0003 was a female aged 11 years at the time of the baseline318 assessment. The subject's height, weight, and BMI (including the age percentile ratings for each measurement) through the study for the 01 January, 01 July, and 31 December age imputations are provided in the following table.

| Subject 052-0003 | | Baseline | | Final: Day 99 | |
|---|---|---|---|---|---|
| | | value | %tile | value | %tile |
| height (cm) | 1-Jan | 148.0 | 48.0 | 149.5 | 45.5 |
| | 1-Jul | | 66.9 | | 64.7 |
| | 31-Dec | | 81.8 | | 80.6 |
| weight (kg) | 1-Jan | 49.0 | 82.4 | 61.0 | 95.2 |
| | 1-Jul | | 87.9 | | 96.9 |
| | 31-Dec | | 92.2 | | 98.1 |
| BMI ($kg/m^2$) | 1-Jan | 22.4 | 89.3-Ov | 27.3 | 97.2-Ob |
| | 1-Jul | | 90.9-Ov | | 97.6-Ob |
| | 31-Dec | | 92.4-Ov | | 98.0-Ob |
| SPD503 dose | | 1 mg | | 4 mg | |

%tile=percentile; Ob=obese BMI; Ov=overweight BMI

During the study, mild TEAEs of weight fluctuation were reported and were ongoing at the time of study discontinuation. At the time of the event of weight fluctuation, the subject was receiving 3 mg SPD503. During the study, mild TEAEs of aggression, mood swings, fatigue, headache, and insomnia were reported. The TEAEs of aggression, mood swings, fatigue, and insomnia were considered to be related to SPD503. The TEAEs of weight fluctuation and headache were considered to be not related to SPD503. On day 99, the subject withdrew from the study for unspecified reasons. The subject previously received methylphenidate hydrochloride for ADHD from 01 Nov 2007 to 19 Feb 2012.

It should also be noted that at a comparable number of subjects had downward shift in BMI between the baseline and final assessment: 17 subjects (7.9%) shifted from a baseline

overweight or healthy BMI to a healthy or underweight BMI at the final assessment: 12 subjects shifted from a baseline overweight BMI to a healthy or underweight BMI at the final assessment and 5 subjects shifted from a baseline healthy BMI to an underweight BMI at the final assessment.

The effects of SPD503 on body weight were assessed based on mean changes in age-adjusted z-scores from baseline and shift analyses of height, weight, and BMI. The changes observed in these growth parameters of age-adjusted z scores over time were not considered clinically meaningful in this subject population considering that patterns of normal human growth are highly complex, nonlinear, and difficult to model (Thalange 1996). Also, subjects who participated in the SPD503-316 study may have been enrolled to the atomoxetine treatment arm. Atoxmoxetine does not affect dopamine to the extent of amphetamines and other stimulant-based drugs used to treat individuals with ADHD but it does increase stimulation by increasing norepinephrine, which can lead to quicker metabolism, more energy, and weight loss. When these subjects enrolled into the SPD503-318 study, the baseline BMI data may have been confounded by this effect as well as the ensuing weight rebound upon discontinuation of atomoxetine.

Considering the results from long-term studies with SPD503 in light of recently published epidemiological findings for the incidence of overweight and obesity in the general population, no apparent signal of risk for weight gain obesity has been observed with SPD503 treatment. The observed shifts in BMI percentile are not in excess of observed shifts from healthy BMI to overweight and obese, or from overweight to obese BMI, among children and adolescents in the general population of Europe and the US over a similar duration of follow-up (Hughes 2011; Marcus 2012; Cunningham 2014; Araujo 2014).

CHMP comment:
It is difficult to draw firm conclusions regarding weight increase and BMI without a control group. The data confirm what has been observed before in the trials, i.e. that Intuniv may induce weight gain and obesity. The US paediatric population is not considered a relevant reference population for this European study population.

The SmPC already include a warning that weight increase /risk of obesity should be evaluated every 3 months in the first year of treatment, and every 6 months in the period thereafter. These data underscore the importance of this warning

Issue solved.