GUANFACINE extended release: daytime sleepiness outcomes from a phase 3 clinical study in adolescents with attention-deficit/hyperactivity disorder

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INTRODUCTION

• Guanfacine extended-release (GXR), a long-acting, non-stimulant, α2C-adrenergic receptor agonist,1,2 is approved as a monotherapy or adjunctive therapy to stimulants for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged ≥ 6–17 years in the USA and ≥ 6–12 years in Canada.

• A phase 3 study (SPD503-312) demonstrated that GXR was more effective than placebo in reducing ADHD Rating Scale IV (ADHD-RS-IV) total scores from baseline to endpoint (primary outcome) in adolescents aged 13–17 years.3

• GXR is associated with sedation-related adverse events.4

OBJECTIVE

• To report on Pediatric Daytime Sleepiness Scale (PDSS) scores and sedation-related treatment emergent adverse events (TEAEs) in a phase 3 study of GXR in adolescents with ADHD (SPD503-312).

METHODS

Study design

• SPDS503-312 was a 13-week, randomized, double-blind, multicentre, parallel-group, dose-optimized, phase 3 study comparing GXR with placebo (Figure 1).

• This study enrolled adolescents (aged 13–17 years) with a primary diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Tred Revision criteria.

• Eligible participants had a baseline ADHD-RS-IV total score of at least 20 and a baseline Clinical Global Impressions-Severity (CGI-S) score of at least 4.

• Participants were enrolled at 48 sites in the USA; four additional sites conducted screening but did not enrol patients.

• Individuals were randomized to receive once-daily GXR or placebo for a 2-week dose-optimization period followed by a 6-week dose-maintenance period.

• During the optimization period, the GXR dose was adjusted until an ‘acceptable’ response was achieved, defined as at least a 30% reduction from baseline in ADHD-RS-IV total score and a Clinical Global Impressions-Improvement (CGI-I) score of 1 or 2, with tolerable side effects.

• The maximum GXR dose was in the range of 4–7 mg/day (up to 0.12 mg/kg/day), depending on patient weight and tolerance of the drug.

Analysis of sedation-related outcomes

• In SPDS503-312, self-reported daytime sleepiness was a secondary outcome that was assessed using the PDSS questionnaire at baseline and throughout the treatment period.

• The questionnaire consists of eight questions that are scored using a 0–5 numeric scale.

• TEAEs relating to sedation (i.e. somnolence, sedation and hypersomnia), was considered of clinical importance.

RESULTS

Patient demographics and baseline characteristics

• In total, 314 individuals were randomized to GXR (n = 157) or placebo (n = 157). Of these, 312 were included in both the full analysis set (FAS) and the safety population (GXR, n = 157; placebo, n = 157), and 227 completed to visit 13 (GXR, n = 157; placebo, n = 110).

• Patient demographics and baseline characteristics in the GXR and placebo groups are similar (Table 1).

• The mean (standard deviation) [SD] optimal and weight-adjusted doses of GXR at visit 8 were 4.3 (1.5) mg and 0.073 (0.048) mg/kg, respectively.

Pediatric Daytime Sleepiness Scale total score

• The changes from baseline in mean PDSS total score for GXR and placebo groups at each study visit are shown in Figure 2.

• A negative change in PDSS score indicates a reduction in self-reported daytime sleepiness compared with baseline.

• The difference (GXR minus placebo) in least-squares (LS) mean change from baseline was statistically significant (p = 0.038; effect size, 0.26) at visit 12 only, not at study endpoint.

Table 1. Key demographics and baseline disease characteristics (safety population, N = 312).5

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GXR (n = 157)</th>
<th>Placebo (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>13.7 (0.8)</td>
<td>13.4 (0.9)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>103 (65.6)</td>
<td>99 (63.9)</td>
</tr>
<tr>
<td>Race, white, n (%)</td>
<td>113 (72.0)</td>
<td>114 (73.5)</td>
</tr>
<tr>
<td>BMI, kg/m2, mean (SD)</td>
<td>22.0 (3.4)</td>
<td>21.8 (3.2)</td>
</tr>
<tr>
<td>Baseline ADHD-RS-IV total score, mean (SD)</td>
<td>39.8 (5.1)</td>
<td>40.3 (6.1)</td>
</tr>
</tbody>
</table>

The safety population comprised of individuals who were randomized and took at least one dose of study drug. ADHD-RS-IV for ADHD Rating Scale IV; BMI, body mass index; GXR, guanfacine extended release; SD, standard deviation.

CONCLUSIONS

In this study, GXR was generally well tolerated and the safety profile was similar to that seen in other studies of GXR.

• Despite the higher incidence of sedation-related adverse events in the GXR group (at doses up to 7 mg/day) than in the placebo group, there was no difference in the PDSS total score between the two groups throughout the treatment period, with the exception of visit 12.6

• All GXR-related adverse events were transient and resolved during the study period.

REFERENCES

5. Guanfacine prescribing information. Available from: http://pi.shirecontent.com/PI/PDFs/Intuniv_USA_ENG.

Disclosures

Guanfacine is an analogous of Sepracor Development LLC and small film or steel stock is Aghni is an employee of Shire. The following authors have received compensation for writing or consulting or speaking fees, or for the radiology they radiate work for certain research support or applies for the computer software or education. The following authors are on the advisory board for Alnylam, Sunovion, Alexion and Alnylam 0016, Neuramicon, Neus-head, Noven, Otsuka, Teva, Parke-Davis, F. Hoffmann-La Roche, AstraZeneca, Bristol-Myers Squibb, Sanofi, Takeda, and Janssen. Zimmerman: Johnson & Johnson PhD. Yuexi Therapy, Neuramicon, Neus-head, Noven, Otsuka, Teva, Parke-Davis, F. Hoffmann-La Roche, AstraZeneca, Bristol-Myers Squibb, Sanofi, Takeda, and Janssen. Zimmerman: Johnson & Johnson PhD. Yuexi Therapy, Neuramicon, Neus-head, Noven, Otsuka, Teva, Parke-Davis, F. Hoffmann-La Roche, AstraZeneca, Bristol-Myers Squibb, Sanofi, Takeda, and Janssen. Zimmerman: Johnson & Johnson PhD. Yuexi Therapy, Neuramicon, Neus-head, Noven, Otsuka, Teva, Parke-Davis, F. Hoffmann-La Roche, AstraZeneca, Bristol-Myers Squibb, Sanofi, Takeda, and Janssen.

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Figure 2. Change from baseline in mean (SD) PDSS total score at each study visit (safety population, N = 312).

<table>
<thead>
<tr>
<th>Visit</th>
<th>GXR (n = 157)</th>
<th>Placebo (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>147 (0.6)</td>
<td>120 (0.74)</td>
</tr>
<tr>
<td>2</td>
<td>14 (2.2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>3</td>
<td>123 (0.9)</td>
<td>85 (0.51)</td>
</tr>
<tr>
<td>4</td>
<td>9 (5.7)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>5</td>
<td>21 (13.4)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>6</td>
<td>2 (0.0)</td>
<td>0 (0.00)</td>
</tr>
</tbody>
</table>

Table 2. Frequently occurring (≥ 5%) TEAEs (safety population, N = 312).

<table>
<thead>
<tr>
<th>TEAE</th>
<th>GXR (n = 157)</th>
<th>Placebo (n = 157)</th>
</tr>
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<tbody>
<tr>
<td>Dizziness</td>
<td>25 (15.9)</td>
<td>16 (10.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>12 (7.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14 (8.9)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18 (11.5)</td>
<td>9 (5.8)</td>
</tr>
<tr>
<td>Dizziness postural</td>
<td>8 (5.1)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (5.7)</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (5.7)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Irritability</td>
<td>11 (7.0)</td>
<td>6 (3.9)</td>
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<td>11 (7.0)</td>
<td>6 (3.9)</td>
</tr>
</tbody>
</table>

TEAEs reported by ≥ 5% of participants in any treatment group

• The changes from baseline in mean PDSS total score for GXR and placebo at each study visit are shown in Figure 2.

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• The difference (GXR minus placebo) in least-squares (LS) mean change from baseline was statistically significant (p = 0.038; effect size, 0.26) at visit 12 only, not at study endpoint.

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