Clinical efficacy of guanfacine extended-release among children and adolescents with primarily inattentive subtype of attention-deficit/ hyperactivity disorder: results from four phase 3 studies

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Objective

To evaluate the efficacy of GXR in children and adolescents with predominantly inattentive ADHD in two dose-optimized and two forced-dose, double-blind, phase 3 studies.

Methods

Study design

Dose optimized studies

• Study SPD503-301 was conducted at centres throughout the USA,5
– Adolescents (aged 13–17 years) with an ADHD-RS-IV total score of at least 32 and a CGI-S score of 3–5 (1:1:1) were randomized to placebo, GXR or ATX and followed up for 3 weeks of downward tapering.
– 4-week (children) or 7-week (adolescents) dose-optimization period was followed by a 6-week dose-stabilization period.
– 3 safety and tolerability evaluations were conducted: week 1, week before tapering with a valid ADHD-RS-IV score.

• Study SPD503-316 was conducted at centres across the USA, Canada and Europe.1
– Children (aged 6–12 years) and adolescents (aged 13–17 years) with ADHD-RS-IV total score of at least 32 and a CGI-S score of 3–5 (1:1:1:1:1) were randomized to GXR 1 mg/day, 2 mg/day, 3 mg/day, 4 mg/day or placebo.
– A 4-week (children) or 7-week (adolescents) dose-optimization period was followed by a 6-week dose-stabilization period.
– For ATX, patients weighing less than 70 kg began on 0.5 mg/day, with a target dose of 1.2 mg/kg/day, but not exceeding 1.4 mg/kg/day; patients weighing 70 kg or more received 40, 60 or 100 mg/day.

Flexible-dose studies

• Study SPD503-301 was conducted at centres throughout the USA;5
– Children and adolescents (aged 6–17 years) with ADHD were randomized (1:1:1:1:1) to GXR 2 mg/day, 3 mg/day, 4 mg/day, or placebo.

Results

Study populations

The numbers of patients randomized and the numbers completing the studies are shown in Table 1.

Integrated dose-optimized studies

In the integrated dose-optimized studies (SPD503-312 and SPD503-310), the difference between GXR and placebo in least-square (LS) mean change in ADHD-RS-IV total scores from baseline to endpoint was statistically significant in patients with predominantly inattentive ADHD (p < 0.01; effect size 0.481) as well as in those with predominantly hyperactive-impulsive or combined subtypes of ADHD (p < 0.001; effect size 0.624) (Figure 1).

Disclosures

B. Adeyi and B. Dirks are employees of Shire, and hold stock and/or stock options. M. Huss is a member of the board of directors for ADHD, St. Luke’s, Medica, Stelara and Stelara, and has received consultancy fees from Lundbeck, Shire, Stelara, and Janssen. A. Cutler has received consultancy fees from Lundbeck, Shire, Stelara, Janssen, and Shire, and has been a member of advisory boards for Janssen, Shire, and Sunovion. A. Hervas has been a member of advisory boards for Janssen, Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, and Shire. K. McBurnett received research support from Abbott Laboratories, Cephalon, Inc., Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, Lundbeck, Medice Arzneimittel, Neos Therapeutics, Otsuka, and Shire. A. Cutler has received consultancy fees from Actelion, Eli Lilly, Medice and Shire. A. Hervas has been a member of advisory boards for Janssen, Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, and Shire. A. Cutler has received research support from Abbott Laboratories, Cephalon, Inc., Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, Lundbeck, Medice Arzneimittel, Neos Therapeutics, Otsuka, and Shire. A. Hervas has been a member of advisory boards for Janssen, Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, and Shire. A. Cutler has received research support from Abbott Laboratories, Cephalon, Inc., Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, Lundbeck, Medice Arzneimittel, Neos Therapeutics, Otsuka, and Shire. A. Hervas has been a member of advisory boards for Janssen, Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, and Shire. A. Cutler has received research support from Abbott Laboratories, Cephalon, Inc., Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, Lundbeck, Medice Arzneimittel, Neos Therapeutics, Otsuka, and Shire. A. Hervas has been a member of advisory boards for Janssen, Eli Lilly and Company, Johnson & Johnson, McNeil Consumer Healthcare, and Shire.

References


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Integrated forced-dose studies

In the integrated forced-dose studies (SPD503-301 and SPD503-304), the difference between GXR and placebo in LS mean change in ADHD-RS-M total scores from baseline to endpoint was statistically significant in patients with predominantly inattentive ADHD for GXR doses of 2–4 mg/day (p < 0.05; effect size 0.463–0.665) and in those with predominantly hyperactive-impulsive or combined subtypes of ADHD for GXR doses of 4 mg/day (p < 0.001; effect size 0.537–0.812) (Figure 2).

– The difference (GXR minus placebo) in LS mean change in ADHD-RS-IV total scores from baseline to endpoint was not statistically significant in patients with predominantly inattentive ADHD treated with GXR 1 mg/day; however, only 12 patients received this dose.

Conclusions

– In children and adolescents with predominantly inattentive ADHD, GXR efficacy was demonstrated in two integrated analyses of phase 3 studies.
– These results indicate that GXR treatment is effective in children and adolescents across predominantly inattentive and hyperactive-impulsive subtypes of ADHD.
– Efficacy across subtypes indicates that GXR treatment has a specific effect on ADHD symptoms and not a general sedative effect on hyperactive-impulsive symptoms.
– These results are supported by phase 3 observations of similar improvements in scores achieved in the Inattention and Hyperactivity/Impulsivity subscales of the ADHD-RS-M in patients receiving GXR.1,2

Table 1. Numbers of patients randomized and the numbers completing the studies

Flexibl-dose studies

<table>
<thead>
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<th>Study</th>
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Forced-dose studies

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<tr>
<td>SPD503-304</td>
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*Patients completing the studies were those who attended all visits up to the last visit before tapering (visit 13 in SPD503-312; visit 15 in SPD503-310). ATE, all-treated; GXR, guanfacine extended-release; N/A, not applicable; PBO, placebo.

Figure 1. Integrated dose-optimized studies (SPD503-312 [n = 314] and SPD503-310 [n = 338]): placebo-adjusted LS mean change in ADHD-RS-V total scores from baseline to endpoint in GXR-treated patients with predominantly inattentive ADHD or predominantly hyperactive-impulsive or combined ADHD

Figure 2. Integrated fixed-dose studies (SPD503-301 [n = 340] and SPD503-304 [n = 338]): placebo-adjusted LS mean change in ADHD-RS-V total scores from baseline to endpoint in GXR-treated patients with predominantly inattentive ADHD or predominantly hyperactive-impulsive or combined ADHD

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