Separating efficacy and sedative effects of guanfacine extended release in children and adolescents with ADHD from four randomized, controlled, phase 3 clinical trials

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Research was funded by Shire Development LLC
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Disclosures

- The following authors have received compensation for serving as consultants or speakers for, or they or the institutions they have worked for have received research support or royalties from, the companies or organizations indicated below:
  - **M Huss**: Actelion, Eli Lilly, Engelhard Arzneimittel, Janssen-Cilag, Medice, Novartis, Shire and Steiner Arzneimittel
  - **A J Cutler**: AbbVie [Abbott], Akili Interactive, Arbor Pharmaceuticals, AstraZeneca, Eli Lilly, Euthymics, Janssen, Johnson & Johnson PRD, Lundbeck, Neos Therapeutics, Neurovance, Novartis, Noven, Otsuka, Pfizer [NextWave], Purdue, Rhodes Pharmaceuticals, Shire, Sunovion, Supernus and Teva
  - **A Hervas**: Eli Lilly, Janssen and Shire
  - **J H Newcorn**: Alcobra, Biobehavioral Diagnostics, Cerecor, Enzymotec, Ironshore, Neos, National Football League, Rhodes, Shire and Sunovion

- **J Gu and B Dirks** are employees of Shire and own stocks or stock options
Guanfacine extended release (GXR)

- Non-stimulant treatment approved for children and adolescents with ADHD
  - USA and Canada: as monotherapy or an adjunct to stimulant therapy
  - Europe: when stimulants are not suitable, not tolerated or have been shown to be ineffective

- In pivotal GXR trials, common TEAEs were somnolence, fatigue and sedation

- To investigate whether sedation may have confounded the efficacy outcomes (i.e. may have accounted for improvement in hyperactivity) in four RCTs in children and adolescents with ADHD, *post hoc* analyses were conducted to compare:
  - time courses of sedative TEAEs and GXR response
  - change in symptoms in individuals with and without sedative TEAEs

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RCT, randomized controlled trial; TEAE, treatment-emergent adverse event
### Study designs: two fixed-dose studies

- **SPD503-301**: randomization to GXR 2, 3 or 4 mg or placebo (1:1:1:1)
- **SPD503-304**: randomization to GXR 1, 2, 3 or 4 mg or placebo (1:1:1:1:1)

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GXR was initiated at 1 mg/day on day 1 and increased weekly by 1 mg until randomized dose was reached (2 mg at week 1, 3 mg at week 2 and 4 mg at week 3). GXR, guanfacine extended release; PBO, placebo.
Study designs: two dose-optimization studies

- **SPD503-312**: randomization to GXR or placebo (1:1)
- **SPD503-316**: randomization to GXR, placebo or ATX (reference) (1:1:1)

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GXR was initiated at 1 mg/day on day 1 and increased weekly by 1 mg until an ‘acceptable’ response (30% reduction from baseline in ADHD Rating Scale IV total score and a Clinical Global Impression-Improvement score of 1 or 2, with tolerable side effects) was achieved. 

ATX dose range was based on participants’ weight at baseline. ATX, atomoxetine; GXR, guanfacine extended release; PBO, placebo.
Time courses of sedative TEAEs and response: pooled SPD503-301 and 304 data

Data are presented by randomized dose.  

*Defined as somnolence, sedation and hypersomnia.

*Defined as having ≥ 30% reduction from baseline in ADHD Rating Scale IV total score; analysis based on last observation carried forward. GXR, guanfacine extended release; PBO, placebo; TEAE, treatment-emergent adverse event.
ADHD-RS-IV total score in patients with and without reported sedative TEAEs

<table>
<thead>
<tr>
<th></th>
<th>Without sedative TEAEs</th>
<th>With sedative TEAEs</th>
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<tbody>
<tr>
<td><strong>SPD503-301 and 304</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.49</td>
<td>0.17</td>
</tr>
<tr>
<td>n = 297a</td>
<td>n = 193a</td>
<td></td>
</tr>
<tr>
<td>GXR</td>
<td>0.67</td>
<td>0.31</td>
</tr>
<tr>
<td>n = 124</td>
<td>n = 132</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>n = 17</td>
<td>n = 51</td>
</tr>
</tbody>
</table>

- GXR significantly reduced ADHD-RS-IV total score compared with placebo in the absence of sedative TEAEs

*p < 0.001. Data based on last observation carried forward. LS means, effect sizes and p values are based on type III sum of squares from an ANOVA model for the change from baseline, including treatment group, age group, study, and pooled country (SPD503-312 and 316 only) as fixed effects, and baseline value as a covariate. Sedative events: somnolence, sedation and hypersomnia. aAll GXR doses combined. ADHD-RS-IV, ADHD Rating Scale IV; GXR, guanfacine extended release; LS, least-squares; NS, not significant; TEAE, treatment-emergent adverse event
Summary and conclusions

The results presented suggest that:

- the time-courses of sedative TEAEs and treatment response with GXR were independent in these studies (i.e. sedation occurred early and typically preceded response)
- GXR significantly reduces ADHD symptoms in patients without sedative TEAEs

These findings from group analytic approaches are relevant for the majority of patients, but may not fully explain trajectories of response and tolerability in individual patients.

Overall, these findings suggest that sedation does not account for the symptomatic improvement associated with GXR.

GXR, guanfacine extended release; TEAE, treatment-emergent adverse event
Acknowledgements

- Under the direction of the authors, David Gothard and Isabelle Kaufmann, employees of Oxford PharmaGenesis, provided writing assistance for this presentation. Editorial assistance in fact checking, copy editing, formatting and proofreading was also provided by Oxford PharmaGenesis.

- Caleb Bliss from Shire Development LLC reviewed and edited the presentation for scientific accuracy.

- Shire International GmbH provided funding to Oxford PharmaGenesis for support in writing and editing this presentation.
Back-up

ADHD-RS-IV subscale scores

ADHD-RS-IV total score by ADHD subtype
GXR improved ADHD symptoms of both inattention and hyperactivity-impulsivity

*\( p < 0.001 \). Data based on last observation carried forward. LS means, effect sizes and \( p \) values are based on type III sum of squares from an ANCOVA model for the change from baseline, including treatment group, age group, study, and pooled country (SPD503-312 and 316 only) as fixed effects, and baseline value as a covariate. \(^a\)All GXR doses combined. ADHD-RS-IV, ADHD Rating Scale IV; GXR, guanfacine extended release; LS, least-squares
GXR significantly improved core ADHD symptoms across the inattentive and combined/hyperactive-impulsive subtypes

***p < 0.001; **p < 0.01; *p < 0.05. Data based on last observation carried forward. LS means, effect sizes and p values are based on type III sum of squares from an ANCOVA model for the change from baseline, including treatment group, age group, study, and pooled country (SPD503-312 and 316 only) as fixed effects, and baseline value as a covariate.

All GXR doses combined. ADHD-RS-IV, ADHD Rating Scale IV; GXR, guanfacine extended release; LS, least-squares