JOHANNES GUTENBERG UNIVERSITÄT MAINZ

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

Michael Huss

Child and Adolescent Psychiatry,
Johannes Gutenberg University Mainz, Mainz, Germany

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Co-authors

- Keith McBurnett,[1] Andrew J Cutler,[2] Amaia Hervas,[3] Joan Gu,[4] Bryan Dirks,[4] Jeffrey H Newcorn[5]

  [1]Department of Psychiatry, University of California, San Francisco, CA, USA

  [2]Florida Clinical Research Center, Bradenton, FL, USA

  [3]Child and Adolescent Mental Health Unit, University Hospital Mútua de Terrassa, Barcelona, Spain

  [4]Shire, Lexington, MA, USA

  [5]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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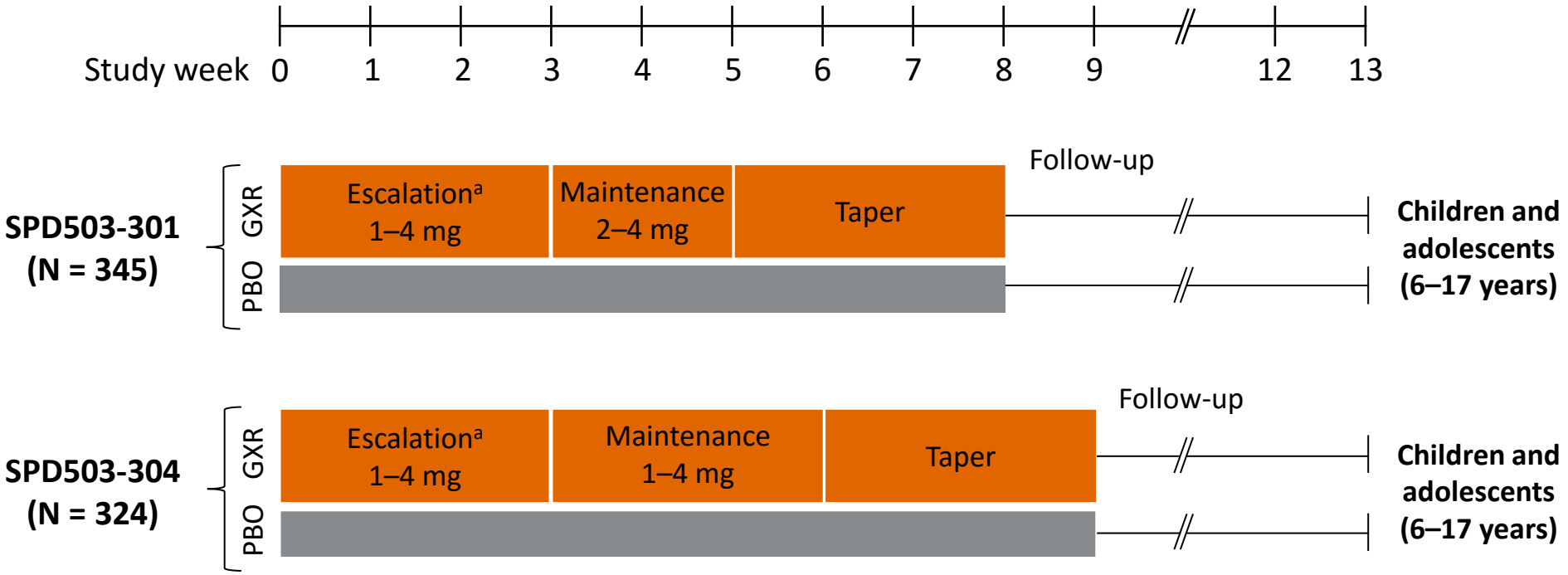
Guanfacine extended release (GXR)

- 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

RCT, randomized controlled trial; TEAE, treatment-emergent adverse event

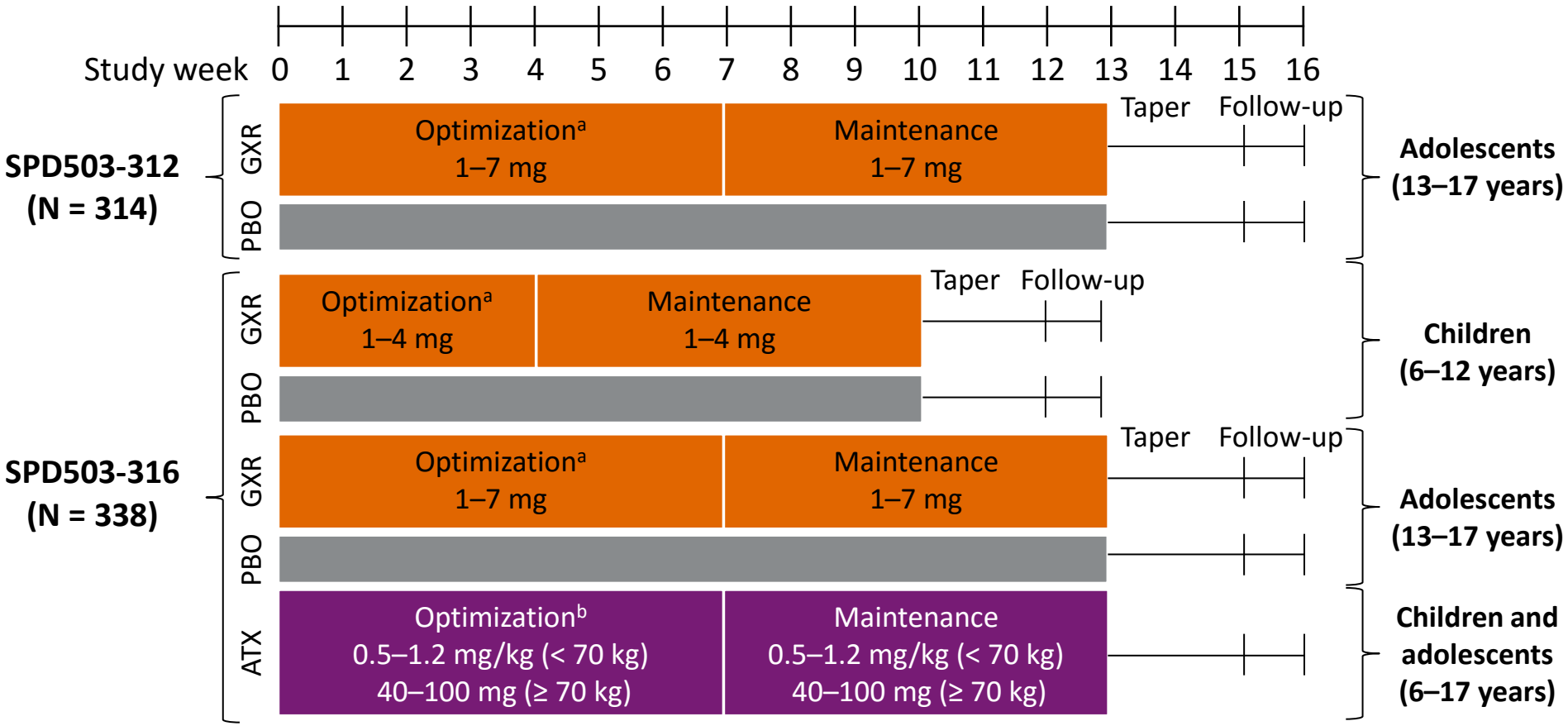
Study designs: two fixed-dose studies



- 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)

[a]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

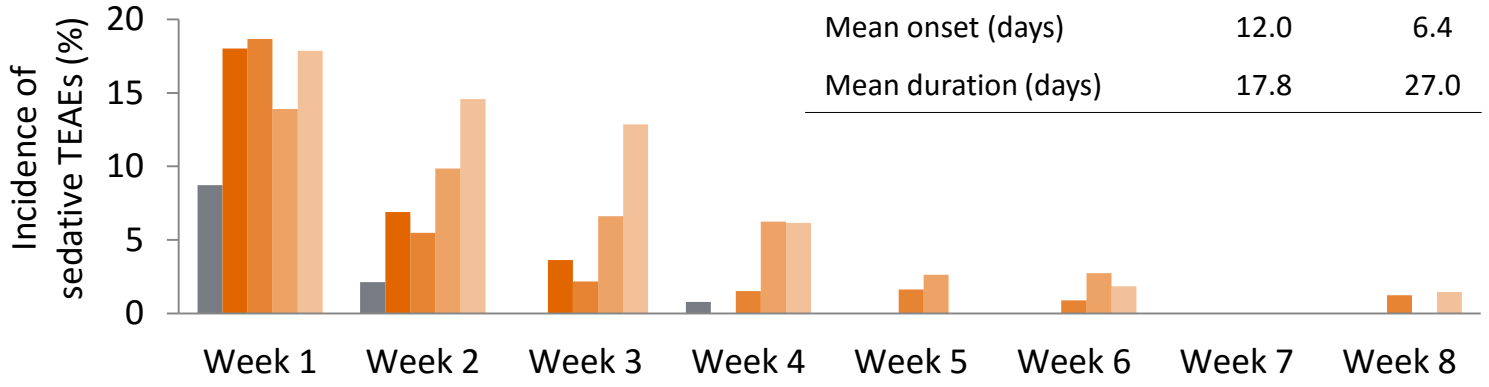


- SPD503-312: randomization to GXR or placebo (1:1)
- SPD503-316: randomization to GXR, placebo or ATX (reference) (1:1:1)

[a]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. [b]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

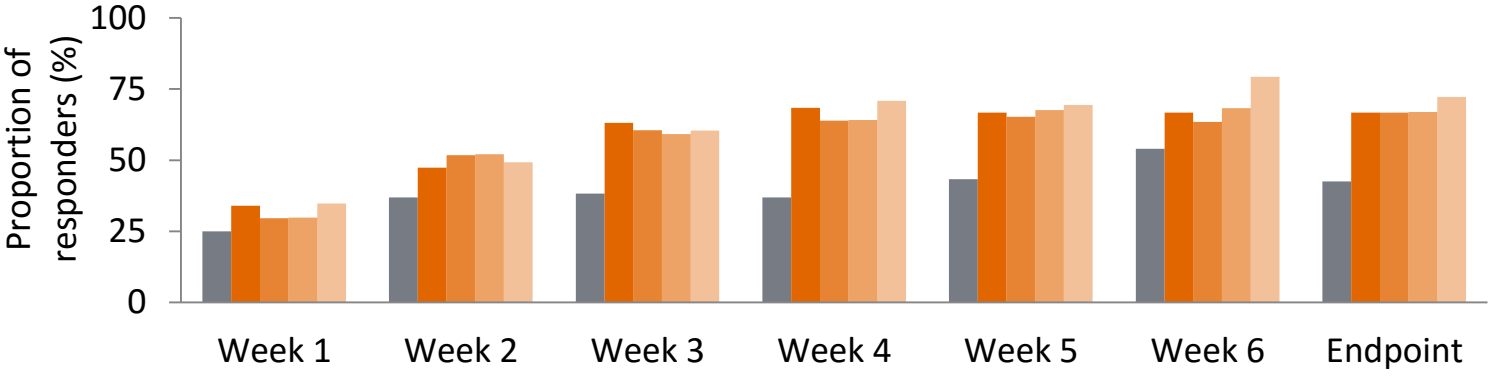
Incidence of sedative TEAEs[a]



	GXR (all doses)	PBO
Mean onset (days)	12.0	6.4
Mean duration (days)	17.8	27.0

PBO (n = 149)
GXR 1 mg (n = 61)
GXR 2 mg (n = 150)
GXR 3 mg (n = 151)
GXR 4 mg (n = 151)

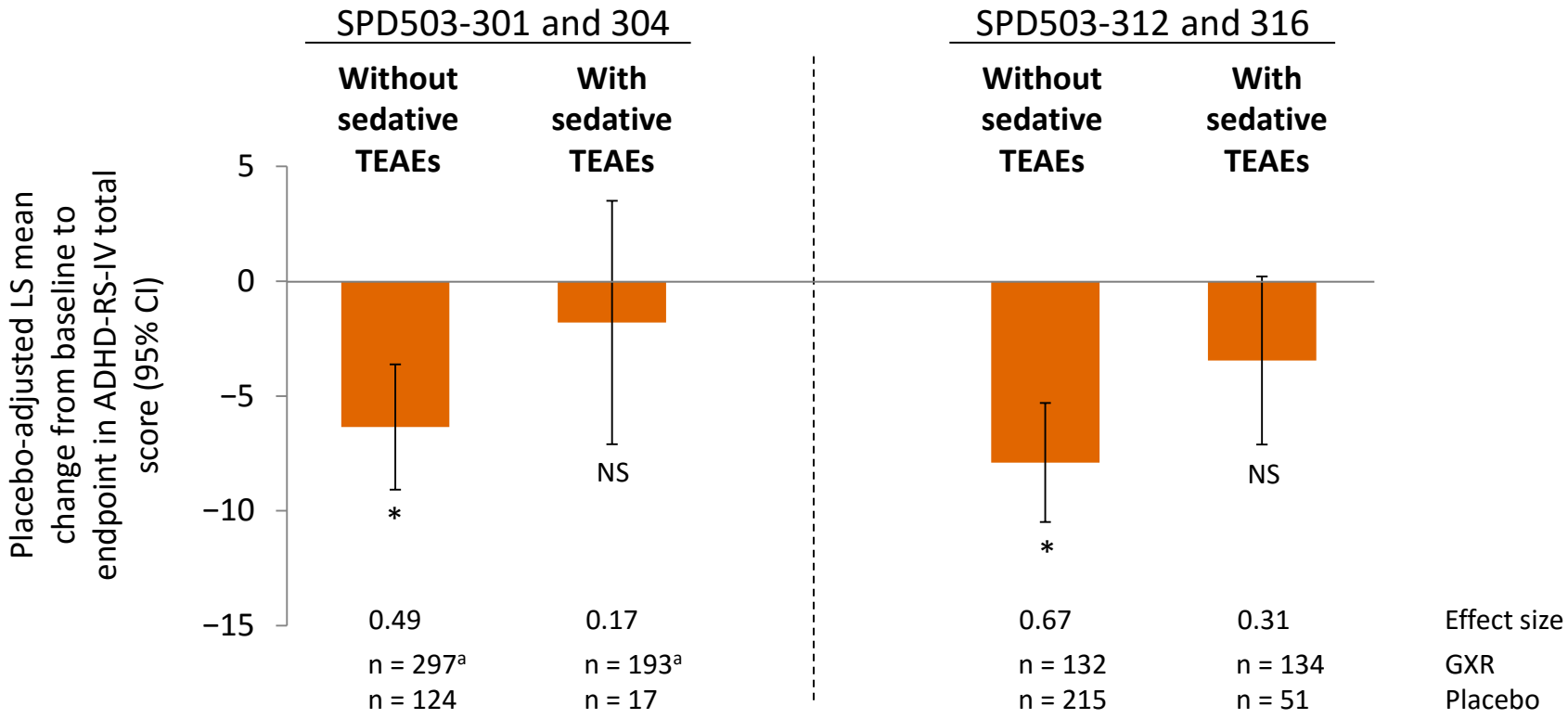
Cumulative treatment response[b]



PBO (n = 141)
GXR 1 mg (n = 57)
GXR 2 mg (n = 147)
GXR 3 mg (n = 142)
GXR 4 mg (n = 144)

Data are presented by randomized dose. [a]Defined as somnolence, sedation and hypersomnia.
[b]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



- 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 ANVOVA 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. [a]All 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

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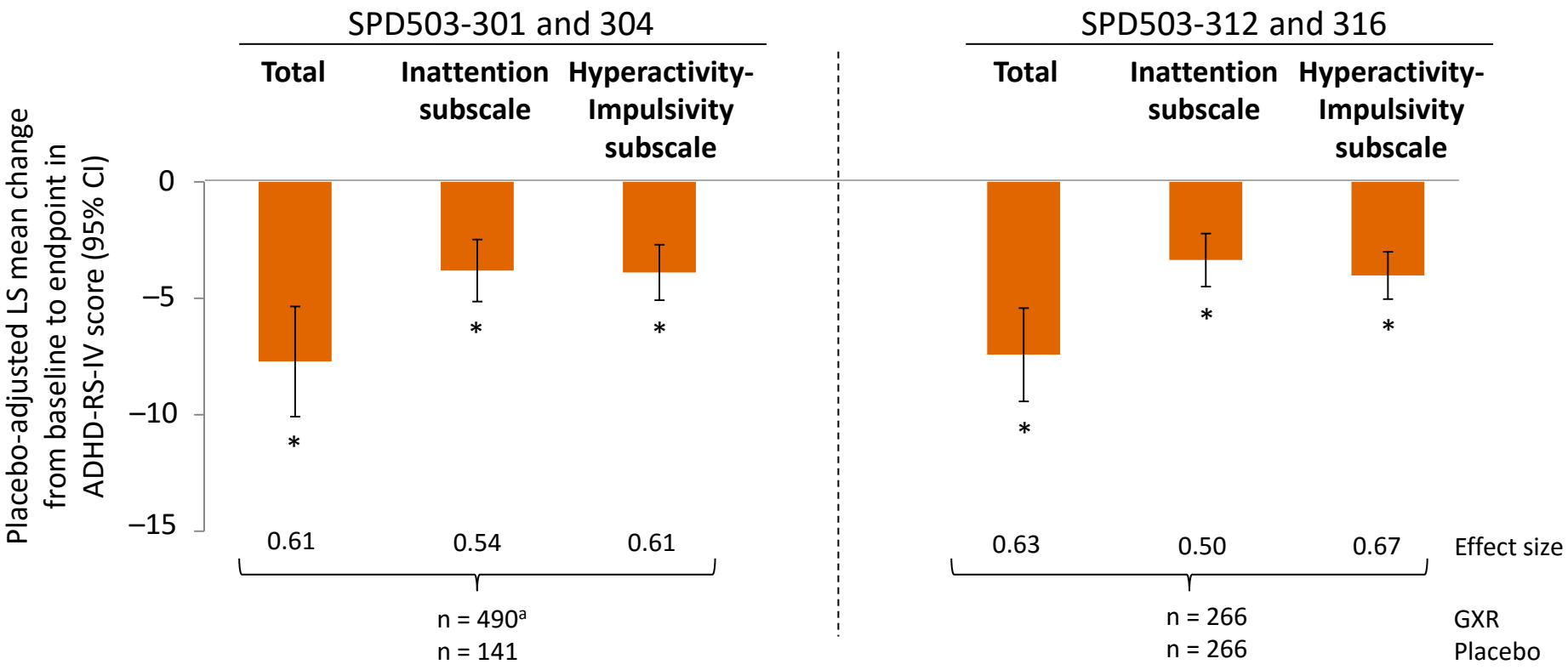
Back-up

ADHD-RS-IV subscale scores

ADHD-RS-IV total score by ADHD subtype

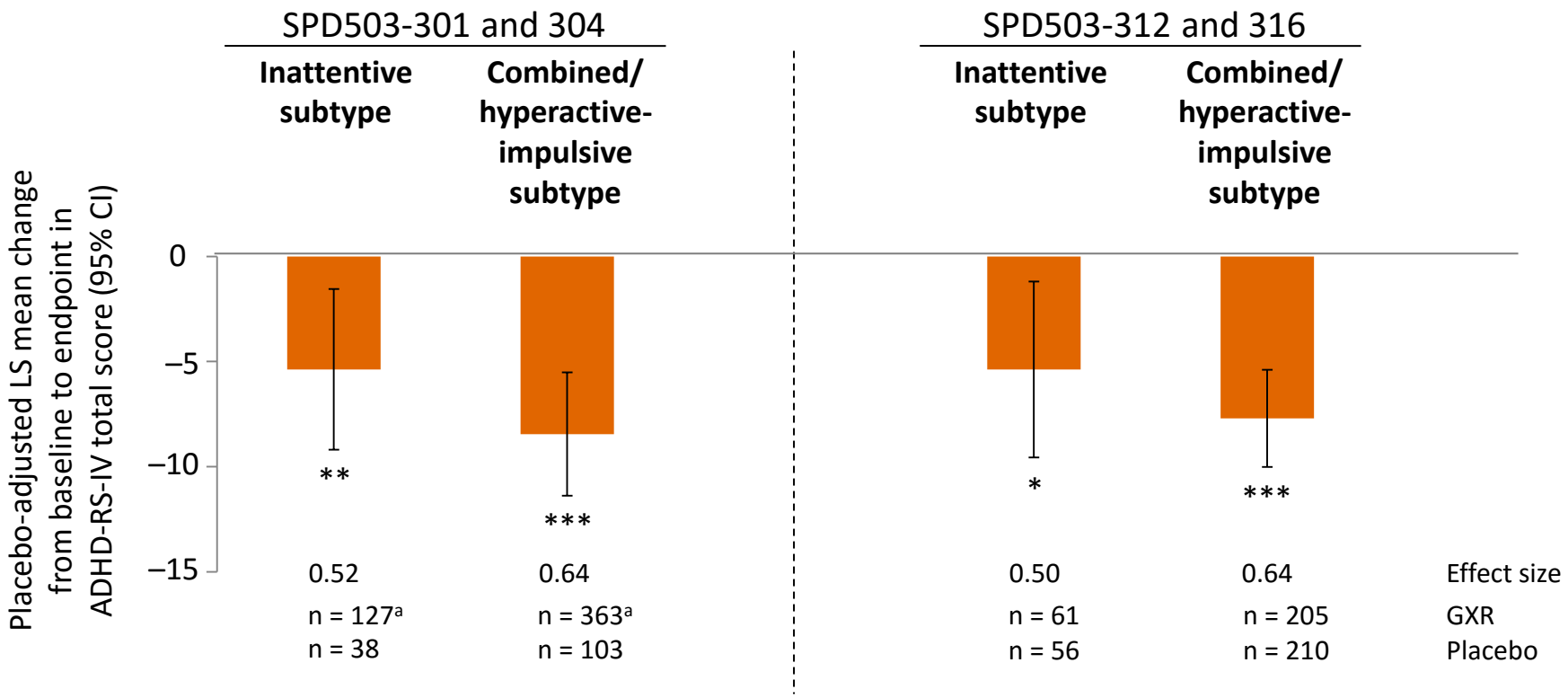
ADHD-RS-IV subscale scores



- 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

ADHD-RS-IV total score by ADHD subtype



- 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.

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