Exploratory Analyses of Efficacy by Sex and Age of a Histamine3 (H3) Receptor Antagonist (Bavisant) for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder

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INTRODUCTION

- Attention deficit hyperactivity disorder (ADHD) is estimated to affect approximately 4% of adults worldwide; however, the actual prevalence may be higher[1].
- Previous studies have shown an influence of sex and age on treatment outcome in adults with ADHD[2]. These factors may have implications on trial design and interpretation of outcomes, as well as in clinical practice. Differential placebo response is also known to influence the overall efficacy results.
- Bavisant (JNJ-31001074) is a selective H3 receptor antagonist, which offers a potential novel mechanism of action for treatment of ADHD[3]. In a phase 2b, dose-ranging study[4], efficacy, safety, and tolerability of 3 doses of bavisant were compared with placebo in adults with ADHD. Although dose-related trends were seen across outcome measures, there was no significant difference vs placebo for any dose tested[4]. Data from this study were used for an exploratory subgroup analysis that examined the potential association of sex and age categories with the efficacy response to treatment with bavisant.

METHODS

Study Population

- Inclusion criteria: Consenting men and women, aged 18-55 yrs (inclusive); body mass index 18-35 kg/m^2 (inclusive); diagnosis of ADHD (DSM-IV-TR criteria, confirmed by the Conners Adult ADHD Diagnostic Interview for DSM-IV); screening Clinical Global Impression – Severity (CGI-S) score ≥4 and a Conners Adult ADHD Rating Scale Self- Report: Screening Version (CAARS-S: SV) DSM-IV ADHD Total Symptoms subscale score based on age and sex: 18 -39 yrs: ≥26 men and ≥32 women; ≥40 yrs: ≥29 men and ≥27 women.
- Exclusion criteria: Current Axis I psychiatric conditions; currently experiencing acute suicidal ideation; history of suicide attempt within the past year or nonresponse to treatment with a psychostimulant medication, atomoxetine or methylphenidate.
- An Independent Ethics Committee at each study site approved the protocol. This study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practices guidelines, applicable regulatory requirements, and in compliance with the respective protocols. All patients provided written informed consent to participate in the study.

Study Design and Intervention

- Design: Randomized, double-blind, placebo- and active- controlled, parallel-group, multicenter study; 37 centers (United States) from April 2009–January 2010. The study consisted of a 14-day screening phase, a 42-day double-blind treatment phase, and a 7-day posttreatment follow-up phase.
- Randomization: with a ratio of 1:1:1:1:1:1 to 1 of 6 treatment groups: placebo, bavisant (1-, 3- or 10- mg/day), atomoxetine hydrochloride (80 mg/day) or OROS methylphenidate hydrochloride (MPH OROS) (54 mg/day). Study centers were to make every attempt to include approximately 4 women for every 10 men randomized; no formal stratification by sex or by age categories was used.
- Dosing: Doses of bavisant were not titrated. Patients on atomoxetine, received 40 mg/day for the first 3 days, and 80 mg/day thereafter; patients on MPH OROS received 36 mg/day for the first 3 days, and 54 mg/day thereafter. No dose reduction was allowed; patients who could not tolerate the full dose were to be discontinued.

Assessments

- Changes in the Attention Deficit Hyperactivity Rating Scale (ADHD-RS-IV)[5] total and subscales (Inattention subscale and Hyperactivity-Impulsivity subscale) scores from baseline were assessed by sex and baseline age categories (18-25 yrs, >25-35 yrs, and >35 yrs) on days 4, 7, 14, 28, and 42.
  - o ADHD-RS-IV is an 18-item (9 items each for inattention and hyperactive-impulsive symptoms) clinician-rated, standardized, validated scale for assessing symptoms of ADHD and response to treatment. Symptoms were rated on a 4-point scale: 0=none, 1=mild, 2=moderate and 3=severe for each item.

Data Analysis

- The intent-to-treat (ITT) analysis set, that included all randomized patients who received ≥1 dose of study drug, and had baseline and at least 1 postbaseline ADHD RS-IV total score, was used for this exploratory analysis.
- Mean (SD) changes from baseline to study endpoint (day 42 Last-observation carried forward [LOCF]) in the ADHD-RS-IV total and subscale scores were calculated by sex and age categories. No statistical comparisons were performed in the subgroup analyses.

RESULTS

Table 1a. Demographic and baseline characteristics by baseline age categories and sex (ITT analysis set)

Characteristic	Age categories			Sex	
	18-25 years (n=119)	>25-35 years (n=129)	>35 years (n=174)	Women (n=181)	Men (n=241)
Age (yrs), mean (SD)	22.1 (2.07)	30.4 (2.77)	44.7 (4.68)	33.8 (11.09)	34.1 (9.51)
Race, n (%)					
White	100 (84)	110 (85.3)	155 (89.1)	151 (83.4)	214 (88.8)
Black/African American	12 (10.1)	9 (7.0)	15 (8.6)	16 (8.8)	20 (8.3)
Ethnicity, n (%)					
Hispanic/Latino	16 (13.4)	13 (10.1)	11 (6.3)	18 (9.9)	22 (9.1)
Weight (Kg), mean (SD)	74.0 (13.85)	79.7 (17.24)	82.5 (16.56)	70.0 (13.69)	86.3 (14.73)
Age at diagnosis (yrs), mean (SD)	13.4 (7.29)	20.2 (11.10)	29.1 (17.85)	22.5 (15.18)	21.6 (14.93)
DSM-iV ADHD subtype, n (%)					
Predominately inattentive	18 (15.1)	34 (26.4)	41 (23.6)	35 (19.3)	58 (24.1)
Predominately hyperactive-impulsive	2 (1.7)	5 (3.9)	2 (1.1)	3 (1.7)	6 (2.5)
Combined type	99 (83.2)	90 (69.8)	131 (75.3)	143 (79.0)	177 (73.4)
Prior psychotropic medication over last 3 months, n (%)	9 (8.0)	12 (9.0)	19 (11.0)	19 (10.0)	21 (9.0)

DSM-IV =Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.

Table 1b. Mean (SD) baseline ADHD-RS-IV total and subscale scores, by baseline age categories and sex (ITT analysis set)

ADHD-RS-IV scales	Age categories			Sex	
	18-25 years (n=119)	>25-35 years (n=129)	>35 years (n=174)	Women (n=181)	Men (n=241)
Placebo (n=73)					
n	23	20	30	30	43
Total	35.7 (9.39)	36.3 (5.83)	35.2 (8.90)	36.9 (9.44)	34.8 (7.30)
Hyperactivity-Impulsivity	14.7 (6.41)	15.3 (3.60)	15.3 (5.93)	16.0 (5.98)	14.5 (5.12)
Inattention	21.0 (3.87)	21.0 (3.17)	19.9 (4.33)	20.9 (4.19)	20.2 (3.68)
Bavisant 1mg (n=68)					
n	19	22	27	22	46
Total	37.8 (10.72)	34.0 (8.23)	35.8 (7.66)	36.4 (7.96)	35.5 (9.21)
Hyperactivity-Impulsivity	17.2 (6.67)	13.5 (5.44)	14.9 (5.74)	14.7 (6.20)	15.2 (5.97)
Inattention	20.6 (4.62)	20.5 (3.86)	21.0 (3.98)	21.7 (2.98)	20.3 (4.46)
Bavisant 3mg (n=68)					
n	21	23	24	36	32
Total	38.0 (9.03)	37.0 (8.28)	36.9 (8.20)	38.6 (9.17)	35.8 (7.24)
Hyperactivity-Impulsivity	17.0 (6.48)	16.2 (6.16)	16.3 (6.02)	17.3 (6.76)	15.5 (5.29)
Inattention	21.0 (4.01)	20.8 (4.03)	20.7 (3.83)	21.3 (3.92)	20.3 (3.85)
Bavisant 10mg (n=72)					
n	13	25	34	36	36
Total	35.6 (8.89)	36.4 (9.46)	34.8 (7.57)	37.0 (9.04)	34.1 (7.57)
Hyperactivity-Impulsivity	15.4 (6.13)	15.3 (6.16)	13.9 (5.97)	15.4 (6.36)	13.9 (5.66)
Inattention	20.2 (3.19)	21.1 (4.36)	20.9 (3.76)	21.6 (4.07)	20.1 (3.51)
OROS MPH 54mg (n=68)					
n	22	22	24	23	45
Total	35.6 (9.53)	36.4 (8.93)	37.1 (7.10)	37.9 (9.09)	35.6 (8.08)
Hyperactivity-Impulsivity	15.9 (6.94)	16.3 (5.33)	17.1 (4.87)	16.9 (6.51)	16.2 (5.30)
Inattention	19.7 (3.78)	20.1 (4.76)	20.0 (3.80)	21.0 (3.52)	19.4 (4.26)
ATOMOX 80mg (n=73)					
n	21	17	35	34	39
Total	37.2 (7.90)	39.6 (9.45)	35.2 (8.18)	38.0 (8.87)	35.8 (8.09)
Hyperactivity-Impulsivity	16.3 (5.12)	17.0 (7.25)	14.7 (5.77)	16.6 (6.58)	14.9 (5.37)
Inattention	20.9 (3.75)	22.6 (3.76)	20.5 (3.82)	21.4 (3.99)	20.9 (3.71)

ADHD-RS-IV=Attention Deficit Hyperactivity Rating Scale; ATOMOX: atomoxetine hydrochloride; ITT: Intent-to-treat; OROS MPH: OROS methylphenidate hydrochloride

- Out of 642 patients screened, 430 were randomized, 422 were included in the ITT set and 335 completed the study.
- The age categories used for the primary analyses were 18-25, >25-35, >35-49 and >49-55. However, as there were few patients (n=29) in the >49-55 years age category, they were combined with the >35- 49 years age category for this analysis.
- None of the bavisant treatments (1-, 3- and 10-mg/day) were significantly superior to placebo in reducing the ADHD-RS-IV total score from baseline to day 42 (primary endpoint[4]); however, both atomoxetine and MPH OROS, included for assay sensitivity, significantly improved the ADHD symptoms, as measured by all scales.

Figure 1. Mean (SD) change from baseline to day 42 (LOCF) in Attention Deficit Hyperactivity Rating Scale (ADHD-RS-IV) total score, by sex

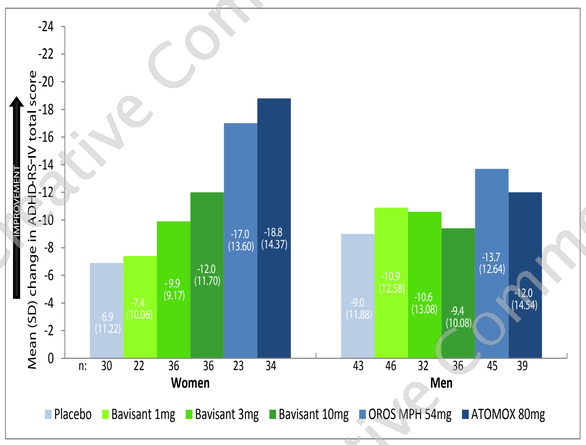
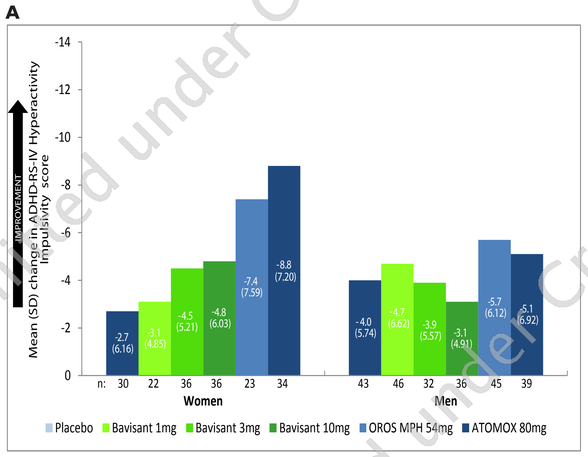


Figure 2. Mean (SD) change from baseline to day 42 (LOCF) in Attention Deficit Hyperactivity Rating Scale (ADHD-RS-IV) subscale scores, by sex

A



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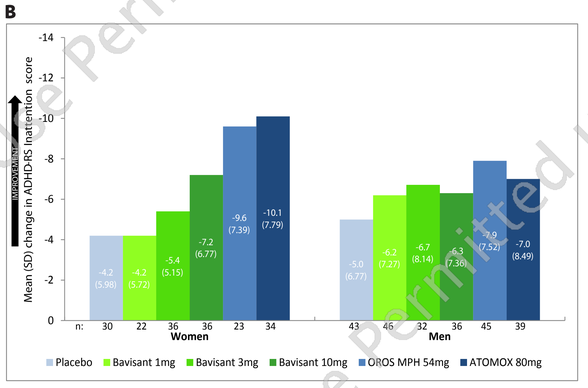
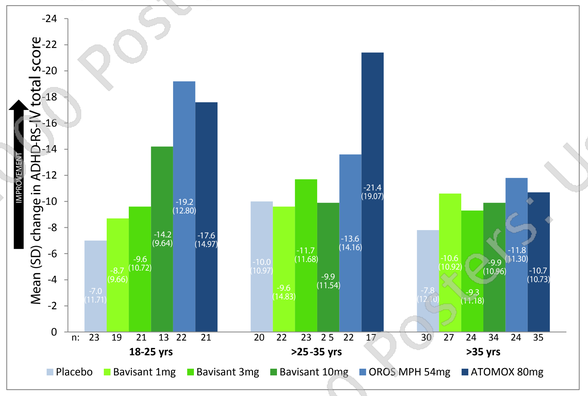


- Women had a lower placebo response than men on ADHD-RS-IV total score and both subscale scores.
- Additionally, women showed an apparent dose-related response to bavisant and greater responses than men to both atomoxetine and MPH OROS in the total and subscales scores of ADHD-RS-IV scale.

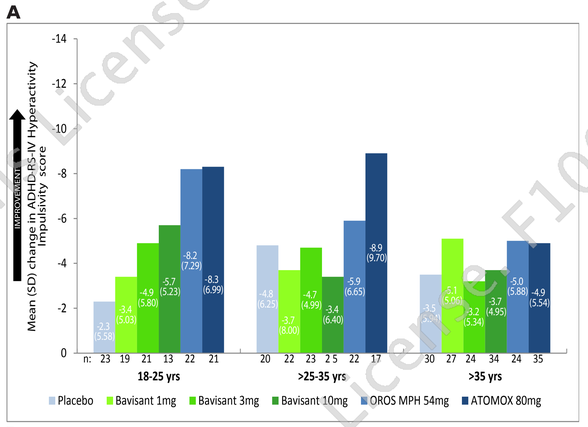
Figure 3. Mean (SD) change from baseline to day 42 (LOCF) in Attention Deficit Hyperactivity Rating Scale (ADHD-RS-IV) total score, by age



- At endpoint, younger patients (<26 years) showed a lower placebo response and a more evident dose-related decrease in ADHD symptoms compared with older patients.
- The oldest age category (>35) generally exhibited less of a response across treatments than the other two age categories.

Figure 4. Mean (SD) change from baseline to day 42 (LOCF) in Attention Deficit Hyperactivity Rating Scale (ADHD-RS-IV) subscale scores, by age

A



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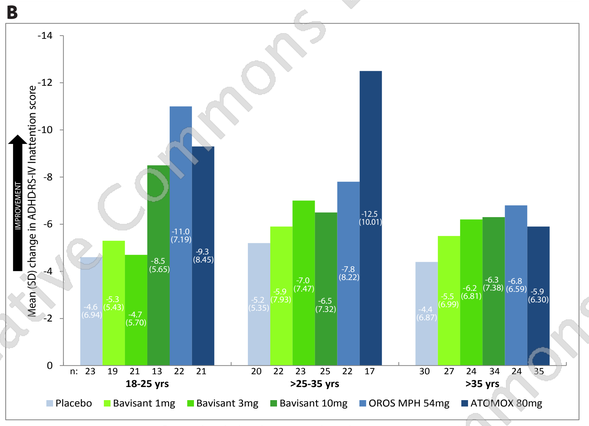

- Patients <26 years of age had the lowest placebo response in the hyperactivity impulsivity subscale of all the age categories, but the placebo response on inattention subscale was comparable among age categories.
- Patients <26 years of age treated with bavisant also showed a dose-related decrease from baseline to endpoint in hyperactivity impulsivity subscale score.
- The oldest age category (>35) generally exhibited less of a response across treatments than any of the other age categories on both subscale scores.

LIMITATIONS

- These findings are limited by the exploratory, post-hoc nature of this subgroup analysis, and by the small size of the subgroups examined. More studies in women and younger patients are warranted to confirm these findings.
- As the treatment randomization scheme was not stratified by sex, the differential placebo response in women compared with men has to be interpreted with caution and that more men were treated with placebo than women must be considered.
- In the earlier primary efficacy analysis from this study, bavisant did not show significant dose-related improvements measured by the change from baseline to endpoint in the ADHD-RS-IV total score (primary efficacy endpoint) and subscale scores[4].

CONCLUSION

- Generally, women and younger patients (<26 years) showed the lowest placebo response.
- Women showed better dose-related improvements with bavisant treatment, as measured by the change in ADHD-RS-IV total and subscale scores. This suggests a differential response profile in women compared with men.
- The improved response profile in younger patients observed in this study is consistent with previous findings of more pronounced efficacy of ADHD medications in children and adolescents[6].
- The sex-related difference in the treatment response observed in this subgroup analysis suggests the potential need to recruit a larger percentage of female patients using a stratified randomization scheme by sex. Additionally, age-related differences seen suggest that, when designing future trials, size of age cohorts may need to be taken into consideration to avoid potential imbalance.
- The findings indicate the presence of a potential association between the baseline characteristics of age and sex and bavisant treatment on efficacy outcomes in ADHD patients.

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DISCLOSURES

Drs. Pandina, Daly, Gassmann-Mayer and Ms Cooper are employees of Janssen Research & Development, LLC. All authors hold stocks in Johnson & Johnson.

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