# Adjunctive Armodafinil in Schizophrenia

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# Abstract

**Background:** Armodafinil, the *R*- and longer-lasting isomer of modafinil, improves wakefulness in patients with excessive sleepiness (ES) associated with treated obstructive sleep apnea (OSA), shift work disorder (SWD), or narcolepsy.[1-4] In patients with schizophrenia, modafinil may improve cognition and other symptoms.[5] This 4-week, double-blind, proof-of-concept study evaluated the efficacy and tolerability of armodafinil as adjunctive therapy in adults with schizophrenia.

**Methods:** Enrolled patients had stable schizophrenia for ≥8 weeks, were receiving oral risperidone, olanzapine, or paliperidone for ≥6 weeks (stable dose for ≥4 weeks), and were randomized to once-daily placebo or armodafinil 50, 100, or 200 mg (initiated at 50 mg and titrated on days 2, 4, and 6). The primary outcome measure was the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery composite score. Secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS).

**Results:** 60 patients were randomized (15 per study group). Mean (SD) age was 43.2 (9.62) years and 73% were men. There were no apparent differences between groups in the MATRICS composite score at final visit: effect sizes (95% confidence interval [CI]) for armodafinil 50, 100, and 200 mg versus placebo were –0.04 (–0.81, 0.73), 0.09 (–0.68, 0.86), and 0.15 (–0.66, 0.95), respectively. There were numerically greater reductions with armodafinil 200 mg versus placebo at final visit in mean PANSS total score (effect size [95% CI]: 0.73 [–0.08, 1.54]) and PANSS negative symptoms score (effect size [95% CI]: 1.69 [0.78, 2.60]). There was no evidence of worsening of positive symptoms in patients in the armodafinil group compared with the placebo group (PANSS positive symptoms score). Armodafinil was generally well tolerated. The most common adverse events reported with armodafinil (all doses) versus placebo, respectively, were: diarrhea (n = 5 versus 1), headache (4 versus 1), and restlessness (3 versus 0). One serious adverse event was reported in a patient receiving placebo.

**Conclusions:** Adjunctive armodafinil 200 mg/day may improve negative symptoms of schizophrenia, without worsening positive symptoms. There was no apparent improvement in cognition. Armodafinil was generally well tolerated. Further investigation in larger studies is warranted.


# Background

- Armodafinil, the *R*- and longer-lasting isomer of modafinil, is a non-amphetamine, wakefulness-promoting medication.[1,6]
- Schizophrenia is a debilitating psychiatric disorder that is associated with psychotic or "positive" symptoms, various deficit or "negative" symptoms, and cognitive impairment.[7]
- Small studies have reported that administration of modafinil may improve some cognitive deficits and other symptoms characteristic of schizophrenia.[8-11]
- The objective of this study was to evaluate the efficacy and safety of armodafinil adjunctive to oral risperidone, olanzapine, or paliperidone therapy in adults with schizophrenia.

# Methods

## Study Design

- A multicenter, 4-week, double-blind, placebo-controlled, parallel-group, fixed-dose, proof-of-concept study was conducted between July and December 2007 at 11 centers in the United States.
- The protocol was approved by local institutional review boards and national/local health authorities. The study was conducted in full accordance with the Good Clinical Practice: Consolidated Guideline.

### Key Inclusion Criteria

- Stable schizophrenia in a nonacute phase for ≥8 weeks
- Oral risperidone, olanzapine, or paliperidone monotherapy for ≥6 weeks prior to screening visit
- Stable dose of antipsychotic for ≥4 weeks
- Age 18–60 years
- Written informed consent

### Key Exclusion Criteria

- Wide Range Achievment Test, 4th ed., reading subtest raw score ≤36
- Calgary Depression Scale for Schizophrenia (CDSS) suicide (item 8) score ≥2
- Moderate-severe depressive symptoms (CDSS score ≥11)
- Positive and Negative Syndrome Scale for Schizophrenia (PANSS) score ≥4 on any positive symptom item
- Modified Simpson-Angus Scale score ≥7
- Barnes Akathisia Scale global score ≥2
- Tardive dyskinesia or other movement disorder
- Active suicidal ideation or imminent risk of self-harm
- Any other Axis I disorder
- Alcohol or substance abuse or dependence within previous 6 months

## Active Drug

- Patients were randomized to receive armodafinil 50, 100, or 200 mg, or placebo, once daily in the morning.
  - Armodafinil was initiated at 50 mg and titrated up by 50 mg on days 2, 4, and 6, as applicable, to the randomized dose.

## Clinical Outcomes

- Primary efficacy variable was mean change from baseline to final visit in MATRICS Consensus Cognitive Battery composite score.
- Secondary efficacy variables included MATRICS domain scores, Clinical Global Impression of Severity of Illness (CGI-S) ratings, Scale for the Assessment of Negative Symptoms (SANS) score, PANSS total and negative scores, and Epworth Sleepiness Scale (ESS).
- PANSS general psychopathology subscale score
- Safety and tolerability measures included adverse events, vital signs, modified Simpson-Angus Scale, Barnes Akathisia Scale, CDSS, clinical laboratory tests, PANSS positive score, and actigraphy data related to sleep.
- Assessments of efficacy and safety/tolerability occurred at baseline and weeks 1, 2, and 4.

## Statistical Analysis

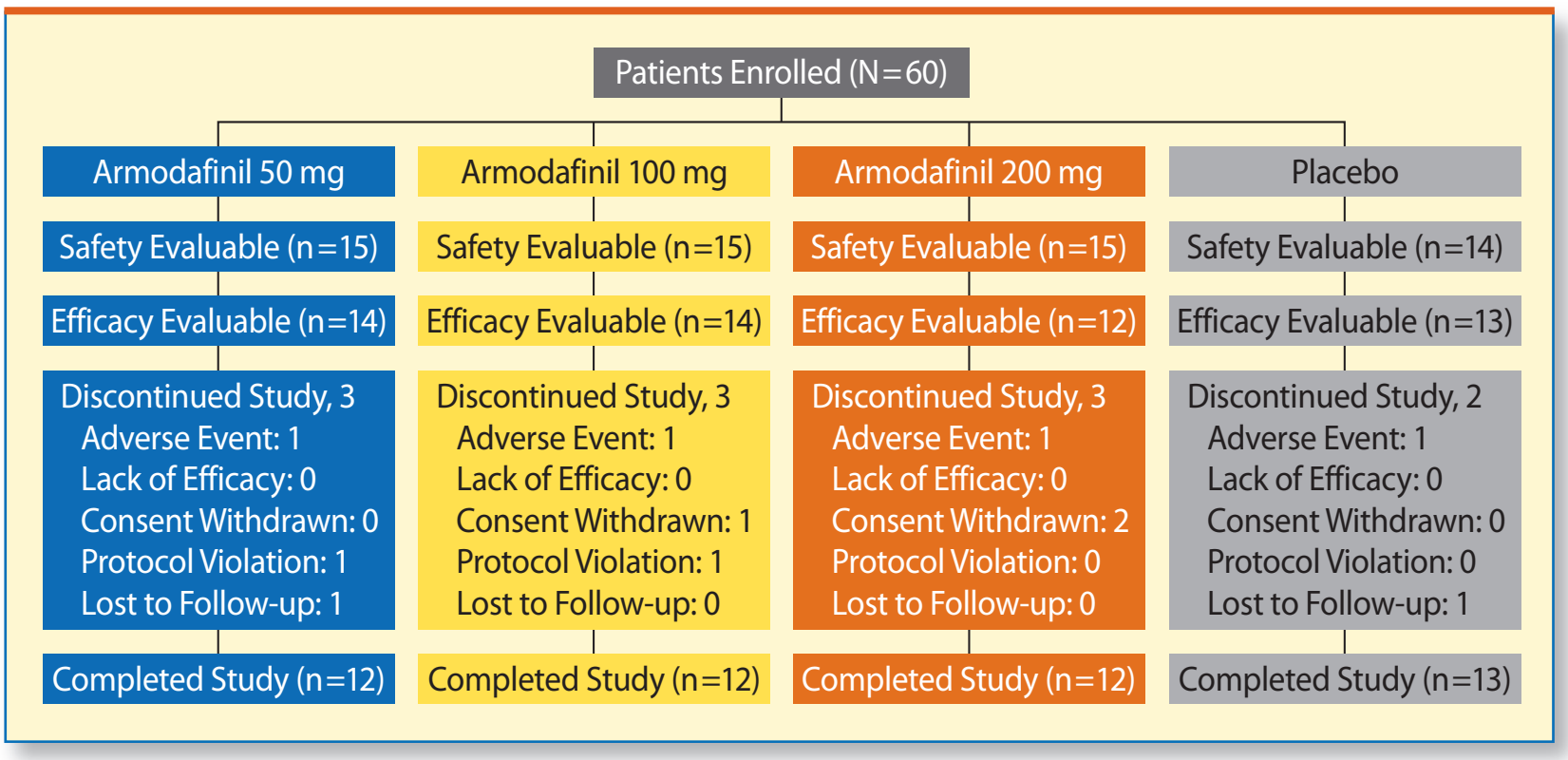
- The safety analysis set included all patients who received ≥1 dose of study drug.
- The efficacy analysis set included all patients in the safety analysis set who had 1 postbaseline assessment on the MATRICS Consensus Cognitive Battery.
- Final visit was calculated using the last-observation-carried-forward method.

# Results

## Patient Disposition and Characteristics

- Of 105 patients screened, 60 were randomly assigned (1:1:1:1) to armodafinil 50 mg (n = 15), 100 mg (n = 15), or 200 mg (n = 15), or placebo (n = 15); 49 patients completed the study **(Figure 1)**.

### Figure 1. Disposition of Patients




- The demographic characteristics of the randomized groups were generally comparable **(Table 1)**.

## Primary Efficacy Variable

- No apparent improvement in cognitive deficits was observed with armodafinil compared with placebo on the MATRICS composite score **(Table 2)**.

## Table 1. Baseline Patient Demographics and Clinical Characteristics

| Variable | Armodafinil 50 mg (n=15) | Armodafinil 100 mg (n=15) | Armodafinil 200 mg (n=15) | Placebo (n=15) |
|---|---|---|---|---|
| Mean age, years (SD) | 44.9 (10.88) | 40.4 (9.58) | 41.4 (9.78) | 46.0 (7.80) |
| Sex, n (%): Male | 11 (73) | 10 (67) | 11 (73) | 12 (80) |
| Female | 4 (27) | 5 (33) | 4 (27) | 3 (20) |
| Race, n (%): | | | | |
| White | 7 (47) | 4 (27) | 5 (33) | 6 (40) |
| Black | 9 (53) | 11 (73) | 9 (60) | 8 (53) |
| Asian | 0 | 0 | 0 | 1 (7) |
| American Indian or Alaskan Native | 0 | 0 | 1 (7) | 0 |
| CGI-S, mean (SD)[a] | 3.3 (0.47) | 3.2 (0.43) | 3.2 (0.58) | 3.2 (0.37) |
| ESS, mean (SD)[a] | 9.4 (5.42) | 7.5 (3.70) | 4.5 (3.23) | 7.5 (6.85) |

CGI-S, Clinical Global Impression of Severity of Illness; ESS, Epworth Sleepiness Scale; SD, standard deviation.
[a]n=14, 14, 12 and 13 for armodafinil 50, 100, 200 mg and placebo, respectively.

## Table 2. Change in MATRICS Composite Score

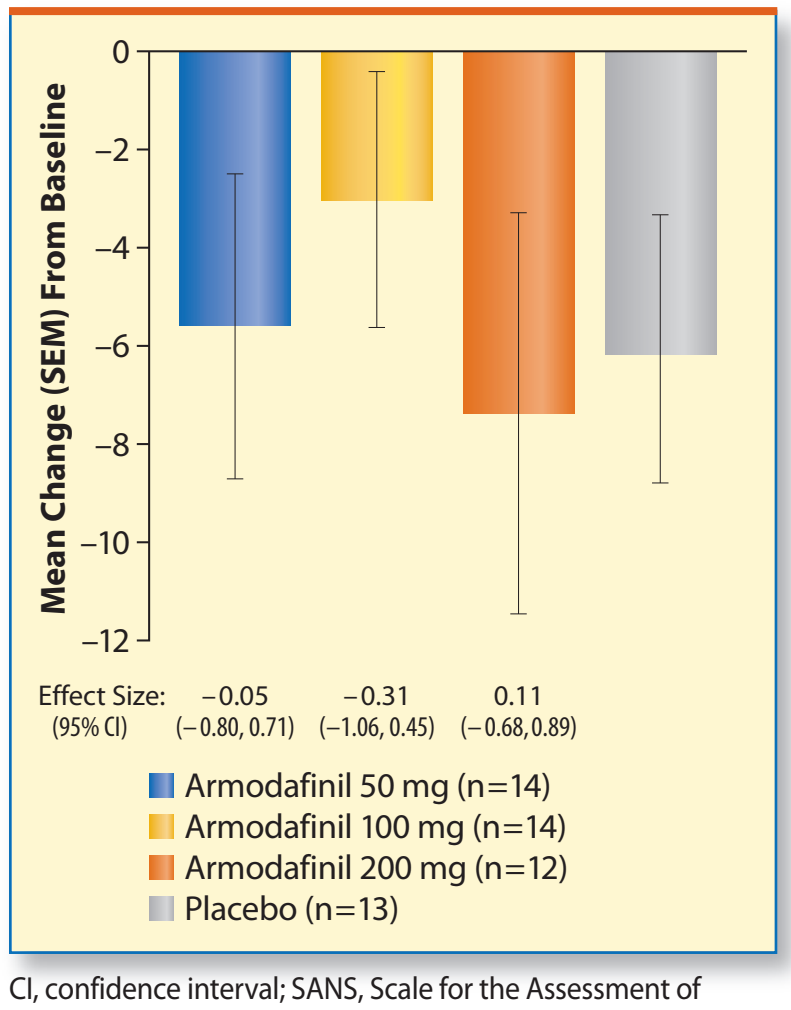
| Variable, mean (SD) | Armodafinil 50 mg (n=14) | Armodafinil 100 mg (n=14) | Armodafinil 200 mg (n=14) | Placebo (n=13) |
|---|---|---|---|---|
| Baseline | 27.8 (8.59) | 20.8 (8.48) | 22.1 (16.44) | 22.3 (14.59) |
| Final visit | 29.6 (11.55) | 23.6 (12.55) | 25.0 (16.51) | 24.5 (12.91) |
| Change from baseline | 1.9 (6.22) | 2.8 (7.98) | 2.9 (4.72) | 2.2 (5.06) |
| Effect size (95% CI) | –0.04 (–0.81, 0.73) | 0.09 (–0.68, 0.86) | 0.15 (–0.66, 0.95) | |

CI, confidence interval; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; SD, standard deviation.

## Secondary Efficacy Variables

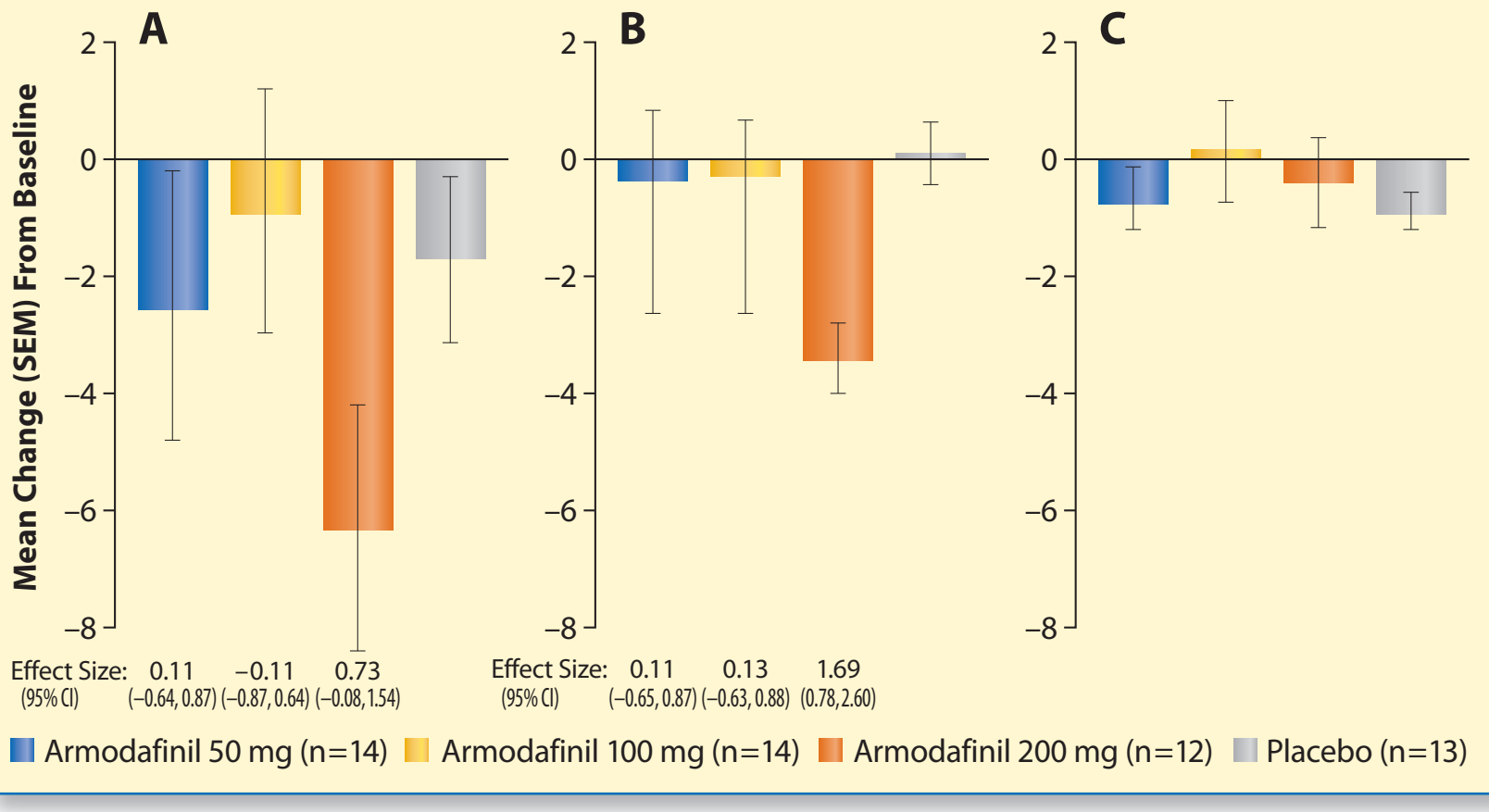
- There was no apparent and consistent effect of armodafinil in any of the MATRICS domain scores (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, or social cognition) at final visit.
- Mean (SD) changes from baseline in CGI-S score were –0.07 (0.27) with armodafinil 50 mg, 0.07 (0.47) with armodafinil 100 mg, –0.17 (0.39) with armodafinil 200 mg, and no change with placebo.
- Results on SANS showed no apparent benefit of armodafinil compared with placebo at final visit **(Figure 2)**.
- The armodafinil 200 mg group showed greater reductions in the PANSS negative symptoms subscale score at final visit without worsening of positive symptoms compared with the placebo group at final visit **(Figure 3)**.
- The effect of armodafinil 200 mg on mean PANSS negative symptoms subscale score was apparent by week 1 **(Figure 4)**.
- Mean (SD) changes in ESS score from baseline to final visit were armodafinil 50 mg, –2.1 (4.87); armodafinil 100 mg, –0.6 (5.36); armodafinil 200 mg, 1.0 (4.43); and placebo, –0.5 (7.48).
- Mean (SD) changes in the general psychopathology subscale score from baseline to final visit were –1.5 (4.8) with armodafinil 50 mg, –0.7 (4.1) with armodafinil 100 mg, –2.1 (3.7) with armodafinil 200 mg, and –0.9 (3.1) with placebo.

### Figure 2. Mean Change in SANS Score




CI, confidence interval; SANS, Scale for the Assessment of Negative Symptoms; SEM, standard error of the mean.

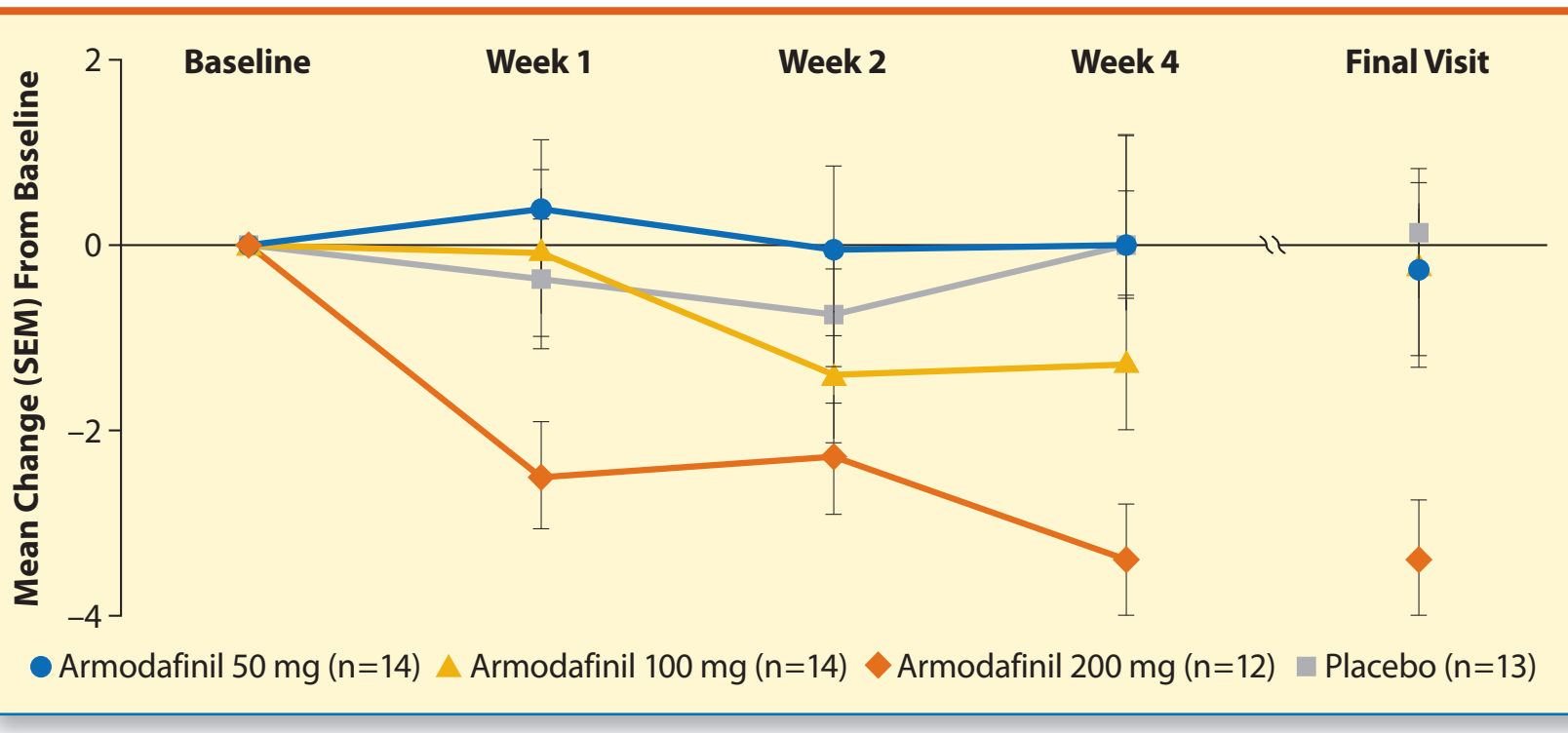
## Figure 3. Mean Change in PANSS Total (A), Negative Symptoms Subscale (B), and Positive Symptoms Subscale[a] (C) Scores




CI, confidence index; PANSS, positive and negative syndrome scale for schizophrenia; SEM, standard error of the mean.

[a]PANSS Positive Score results are from the safety analysis set and include 1 additional patient in each group, except armodafinil 100 mg; effect size was not calculated.

## Figure 4. Mean Change in PANSS Negative Scores[a]




PANSS, positive and negative syndrome scale for schizophrenia; SEM, standard error of the mean.

[a]In the armodafinil 200-mg group, the effect sizes (95% confidence interval) were: 0.89 (0.05, 1.74) at week 1; 0.75 (−0.08, 1.58) at week 2; 1.62 (0.70, 2.55) at week 4; and 1.69 (0.78, 2.60) at final visit.

## Tolerability

- Armodafinil was generally well tolerated; diarrhea and headache were the most commonly reported adverse events among all patients who received any dose of armodafinil **(Table 3)**.
- One patient in each study group discontinued study drug because of an adverse event, including worsening psychosis (placebo), folliculitis (armodafinil 50 mg), hostility (armodafinil 100 mg), and restlessness (armodafinil 200 mg).

### Table 3. Adverse Events in ≥7% of All Patients Who Received Armodafinil

| Variable, n (%) | Armodafinil 50 mg (n=15) | Armodafinil 100 mg (n=15) | Armodafinil 200 mg (n=15) | Placebo (n=14) |
|---|---|---|---|---|
| Diarrhea | 2 (13) | 2 (13) | 1 (7) | 1 (7) |
| Headache | 2 (13) | 0 | 2 (13) | 1 (7) |
| Dizziness | 1 (7) | 1 (7) | 0 | 0 |
| Insomnia | 1 (7) | 0 | 1 (7) | 2 (14) |
| Muscle spasms | 0 | 2 (13) | 0 | 0 |
| Restlessness | 0 | 0 | 3 (20) | 0 |
| Dry mouth | 0 | 1 (7) | 1 (7) | 1 (7) |

- One patient in the placebo group had a serious adverse event of worsening psychosis.
- Psychiatric adverse events included insomnia (2 with placebo, and 1 each with armodafinil 50 and 200 mg), restlessness (3 with armodafinil 200 mg), and hostility (1 with armodafinil 100 mg).
- Mean changes from baseline in pulse and diastolic blood pressure values were slightly higher at each visit in the armodafinil 200 mg group compared with placebo, but these were not considered to be clinically meaningful by the investigators; **Table 4** displays mean changes in vital signs at the final visit.

**Table 4. Change in Vital Signs From Baseline to Final Visit**

| Variable, mean (SD) | Armodafinil 50 mg (n=15) | Armodafinil 100 mg (n=14) | Armodafinil 200 mg (n=14) | Placebo (n=14) |
|---|---|---|---|---|
| Pulse (bpm) | 0.3 (9.98) | –1.1 (9.37) | 1.9 (6.59) | –3.2 (10.81) |
| Sitting SBP (mmHg) | 2.1 (10.84) | 1.4 (12.49) | –0.1 (10.99) | 1.8 (9.15) |
| Sitting DBP (mmHg) | 0.4 (6.48) | 2.7 (9.08) | 4.1 (6.44) | –0.6 (6.36) |

Bpm = beats per minute; DBP = diastolic blood pressure; SBP = systolic blood pressure.

- No differences were found on the Simpson-Angus Scale, Barnes Akathisia Scale, or CDSS; no notable differences were observed regarding laboratory values or electrocardiograms.
- Armodafinil did not worsen the PANSS positive symptoms subscale compared with placebo **(Figure 3C)**.
- Analysis of the actigraphy data indicated that patients receiving armodafinil 200 mg may have had decreased nighttime sleep compared to other armodafinil dosages and placebo **(Table 5)**.

**Table 5. Change in Actigraphy Variables From Baseline to Final Visit**

| Variable, mean (SD) | Armodafinil 50 mg (n=13) | Armodafinil 100 mg (n=14) | Armodafinil 200 mg (n=14) | Placebo (n=13) |
|---|---|---|---|---|
| Sleep latency (min) | –6.4 (20.29) | 3.5 (11.54) | 9.8 (26.56) | –1.4 (10.96) |
| Sleep efficiency (%) | 3.1 (7.77) | –4.8 (7.57) | –5.5 (8.77) | 2.3 (5.98) |
| Total sleep time (min) | 16.3 (97.31) | 19.9 (96.09) | –39.9 (57.29) | 22.7 (107.16) |

# Conclusions

- Armodafinil showed no apparent beneficial effect on cognitive deficits as assessed by the MATRICS Battery.
- Overall results from the CGI-S, SANS, and ESS showed no apparent benefit from armodafinil administration compared with placebo.
- Armodafinil 200 mg may improve the negative symptoms of schizophrenia, as measured by the PANSS negative symptoms subscale, without worsening positive symptoms.
- Armodafinil was generally well tolerated and did not cause or worsen psychotic symptoms, extrapyramidal symptoms, or akathisia.
- The effect of armodafinil 200 mg on negative symptoms of schizophrenia warrants future evaluation in a larger, appropriately powered clinical study.

## References

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