INTRODUCTION

Patients with schizophrenia experience positive symptoms (e.g., hallucinations, delusions, catatonic symptoms, and incoherence of thought), negative symptoms (e.g., social withdrawal and blunted affect), and cognitive deficits. Reportedly, negative symptoms are closely related to functional impairments regarding the maintenance of personal care, performance of household chores, learning, ability to work or attend school, and interacting with others.1,2 Additionally, these symptoms seem to have a greater impact on social functioning than do positive symptoms.3

Conventional antipsychotic drugs do not provide sufficient improvement in negative symptoms; thus, effective treatments to satisfy this unmet need are anticipated.4,5 Because N-methyl-D-aspartate receptor (NMDAR) inhibitors, such as phencyclidine and ketamine, induce not only positive but also negative symptoms and cognitive deficits in healthy adults,6-9 NMDAR dysfunction has been proposed as a factor contributing to the negative symptoms of schizophrenia.10 Therefore, NMDA enhancers, such as glycine reuptake inhibitors (GRIs), may improve negative symptoms.

Bitopertin, a GRI that selectively inhibits a glycine transporter, GlyT1, activates NMDAR by increasing the concentration of glycine in the synaptic cleft.11 A proof-of-concept, global phase II study was conducted to investigate the clinical effect of bitopertin on negative symptoms in patients with schizophrenia.12 A significant improvement was observed in
Figure 1. CONSORT diagram. *some patients were excluded for more than one reason. J: Japanese, N-J: non-Japanese.
the 10-mg and 30-mg groups compared with the placebo group in the per-protocol population, and also a trend toward improvement was observed in the intent-to-treat (ITT) population.

To the best of our knowledge, this was the first global study in the field of psychiatry, led by Europe and the US and in-

Table 1. Analysis populations and baseline characteristics of the ITT population

| Characteristic                        | Placebo | Bitopertin |
|---------------------------------------|---------|------------|
|                                       | J=N=10  | N-J=67     |
| J=10 mg/day                           | N=10    | N-J=71     |
| J=30 mg/day                           | N=9     | N-J=68     |
| J=60 mg/day                           | N=9     | N-J=68     |

Analysis population, N

- All randomized: N=10
- Safety (≥1 dose): N=10
- Intent to treat: N=10
- Modified intent to treat: N=10
- Per protocol: N=10

Demographic

- Male, N (%): 7 (70) 40 (60) 6 (60) 51 (72) 1 (11) 43 (63) 6 (67) 46 (68)
- Age, mean (SD), years: 38 (11) 39 (10) 43 (10) 40 (10) 37 (10) 41 (10) 40 (8) 39 (10)
- BMI, mean (SD), kg/m²: 25 (3) 29 (6) 24 (4) 29 (5) 27 (6) 26 (9) 24 (4) 28 (6)

Primary antipsychotic treatment, N (%)

- Aripiprazole: 2 (20) 6 (9) 2 (20) 7 (10) 3 (33) 7 (11) 2 (22) 6 (9)
- Olanzapine: 2 (20) 19 (28) 2 (20) 21 (30) 1 (11) 20 (29) 2 (22) 20 (29)
- Quetiapine: 1 (10) 9 (13) 2 (20) 10 (14) - 10 (15) 1 (11) 10 (15)
- Risperidone related: 5 (50) 32 (48) 4 (40) 31 (44) 5 (56) 28 (41) 4 (44) 31 (46)
- Paliperidone*: - 10 (15) - 9 (13) - 4 (6) - 4 (6)
- Risperidone (incl. risperidone long-acting injection*): 5 (50) 22 (33) 4 (40) 22 (31) 5 (56) 24 (35) 4 (44) 27 (40)

Benzodiazepine treatment, N (%)

- Total at least one treatment: 1 (10) 19 (28) 8 (80) 17 (24) 5 (56) 17 (25) 8 (89) 18 (26)
- Clonazepam: 1 (10) 5 (7) 2 (20) 5 (7) 3 (33) 4 (6) - 8 (12)
- Lorazepam: 1 (10) 6 (9) - 4 (6) 2 (22) 3 (4) 3 (33) 6 (9)
- Alprazolam: - 4 (6) 1 (10) 6 (8) 1 (11) 5 (7) - 3 (4)
- Diazepam: 1 (10) 2 (3) - 2 (3) - 2 (3) - -
- Flunitrazepam: - - 5 (50) - - - 4 (44) -
- Nitrazepam: - - 2 (20) - 1 (11) - - -
- Quazepam: - - 2 (20) - - - - -
- Triazolam: - - 2 (20) - - - - -
- Brotizolam: 1 (10) - - - - - 2 (22) -
- Bromazepam: - - - - 1 (11) 1 (1) 1 (11) 1 (1)
- Etizolam: - - 1 (10) - - - 1 (11) -
- Lormetazepam: 1 (10) - - - - - 1 (11) -
- Ethyl loflazepate: - - - - - - 1 (11) -
- Flurazepam: - - - - - - 1 (11) -
- Prazepam: - - - - - - 1 (1) -
- Cinolazepam: - 1 (1) - - - - - -
- Estazolam: - - - - - 1 (1) - -
- Temazepam: - 1 (1) - - - - - -
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Table 1. Analysis populations and baseline characteristics of the ITT population (continued)

| Characteristic                                         | Placebo N=10 | N=10 | N-J N=67 | N-J N=71 | N-J N=9 | N-J N=68 | N-J N=68 |
|--------------------------------------------------------|--------------|------|----------|----------|---------|---------|---------|
| **Baseline psychopathology and functioning, mean (SE)** |              |      |          |          |         |         |         |
| PANSS Total score                                      | 83.4 (2.7)   | 79.4 (3.7) | 79.4 (1.1) | 83.4 (3.3) | 79.5 (1.3) | 83.4 (2.6) | 77.9 (1.0) |
| Negative symptom factor score                         | 26.6 (1.4)   | 25.9 (0.4) | 25.8 (0.4) | 28.0 (1.7) | 26.3 (0.5) | 28.7 (1.8) | 26.2 (0.4) |
| Positive symptom factor score                         | 19.2 (0.8)   | 17.4 (0.5) | 17.7 (0.4) | 19.7 (0.9) | 17.6 (0.5) | 18.9 (0.9) | 17.1 (0.4) |
| Disorganized thought/cognition factor score           | 20.8 (1.3)   | 20.6 (0.4) | 21.5 (0.4) | 20.1 (1.6) | 20.8 (0.4) | 19.7 (1.6) | 20.4 (0.3) |
| Uncontrolled hostility/excitement factor score        | 7.5 (0.6)    | 6.6 (0.7) | 6.5 (0.3) | 6.8 (0.7) | 6.6 (0.3) | 6.9 (0.8) | 6.2 (0.3) |
| Anxiety/depression factor score                       | 9.3 (0.5)    | 8.5 (0.9) | 8.0 (0.3) | 8.9 (1.1) | 8.2 (0.4) | 9.3 (0.7) | 8.0 (0.3) |
| CGI-S of negative symptoms                            | 4.9 (0.2)    | 4.8 (0.3) | 4.4 (0.1) | 4.9 (0.4) | 4.4 (0.1) | 4.7 (0.3) | 4.4 (0.1) |
| CPS total score                                        | 36.8 (3.8)   | 43.3 (5.6) | 49.7 (1.5) | 41.6 (4.8) | 53.4 (1.4) | 42.2 (5.7) | 50.9 (1.4) |

*risperidone long-acting injection and paliperidone were not approved in Japan at the time of the study, but were used by some of the non-Japanese patients. BMI: body mass index, CGI-S: Clinical Global Impression of Severity, J: Japanese, N-J: non-Japanese, PANSS: Positive and Negative Syndrome Scale, PSP: Personal and Social Performance scale, SD: standard deviation, SE: standard error

volving Japan. Therefore, examining the impact of the differences between Japanese and non-Japanese patients based on demographic characteristics and social environment on the evaluation of the efficacy and safety of bitopertin may have clinical relevance. This manuscript is a report of a subgroup analysis comparing the efficacy and safety of bitopertin in 38 Japanese patients with those in non-Japanese patients.

**METHODS**

**Study design**

This is a subgroup analysis of data from a global, multicenter, randomized, double-blind, placebo-controlled study conducted between February 2008 and September 2009, including the participation of ten countries: Austria, Brazil, France, Germany, Hungary, Mexico, Poland, Russia, the US, and Japan. The patients were randomized to treatment in Japan and elsewhere separately. The detailed methods were previously published.15

**Study subjects**

According to the recommendations by the National Institute of Mental Health-Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus statement on negative symptoms,13,14 schizophrenic outpatients with chronic stable positive symptoms and prominent negative symptoms were recruited, and patients with uncontrolled extrapyramidal symptoms and depressive symptoms were excluded from the present study. All patients gave informed consent to participate in the study and their anonymity was preserved.

**Drugs**

Bitopertin (10, 30, or 60 mg/day) or placebo was administered once daily, in addition to the primary treatment (one or two antipsychotic drugs, including atypical antipsychotic drugs such as olanzapine, risperidone, quetiapine, aripiprazole, and paliperidone).

**Endpoints**

The primary endpoint was the mean change from baseline in the negative symptom factor score (NSFS) of the Positive and Negative Syndrome Scale (PANSS).15 The secondary endpoints were the PANSS NSFS response rate (≥20% change), other PANSS factor scores, PANSS total score, PANSS symptom scores, Clinical Global Impression-Improvement (CGI-I) of negative symptoms,16 functioning on the Personal and Social Performance scale (PSP),17 and safety.

**Statistical methods**

A mixed-model repeated-measure analysis (MMRM) was used for variables with repeated scheduled measurements. The MMRM model included fixed-effect terms for treatment group, visit week (categorical and nested within patient), baseline score, treatment-by-visit interaction, and the inter-
action between baseline score and visit week. Statistical methods are described in detail in the original paper. Data from Japanese and non-Japanese sites for key efficacy and safety variables were compared in the ITT population. This comparison should be interpreted with caution because of the small number of patients from Japanese sites. Statistical significance was not evaluated. In a post-hoc analysis, the correlations between the PSP total score and the score for each PANSS symptom factor at baseline were examined.

RESULTS

In the original study, 323 of 477 screened patients were randomly assigned to receive placebo or bitopertin (10, 30 or 60 mg/day). Results have been published and other details can be found in the original paper.

Patient demographics and baseline characteristics

Of the 323 patients randomly assigned to treatment, 38 were Japanese: of these, all 38 were included in the ITT population and 34 patients completed the study (Figure 1). Regarding primary antipsychotic treatment, the most commonly used drug was risperidone (47%), followed by aripiprazole (24%) and olanzapine (18%) in Japanese patients. In non-Japanese patients, risperidone-related products were the most common [risperidone, paliperidone, and risperidone long-acting injection, (45%)], followed by olanzapine (29%), quetiapine (14%), and aripiprazole (9%). The proportion of Japanese patients receiving benzodiazepine concomitantly was higher than that of non-Japanese patients (58% versus 26%, respectively) (Table 1).

Efficacy

At week 8 from baseline, an effect of bitopertin 10 mg and 30 mg on negative symptoms was observed in both Japanese (-4.7 and -6.4 in the 10-mg and 30-mg groups, respectively) and non-Japanese patients (-6.7 and -6.4, respectively) on the basis of a greater difference in the change in PANSS NSFS (Table 2). The same trend was observed for PANSS NSFS response rate in both Japanese and non-Japanese patients (Table 2, Figure 2). There was no difference in the change from baseline at week 8 in PANSS NSFS between the bitopertin 60-mg group and the placebo group in Japanese (-2.5 and -3.2, respectively).

Table 2. Primary and secondary endpoints (ITT population)

| End points | Placebo | Bitopertin | 10 mg/day | 30 mg/day | 60 mg/day |
|------------|---------|------------|-----------|-----------|-----------|
| J | N-J | J | N-J | J | N-J | J | N-J |
| PANSS negative symptom factor score (N) | (10) | (67) | (10) | (71) | (9) | (68) | (10) | (68) |
| Change from baseline at wk 8 (SE) | -2.5 (1.2) | -5.5 (0.6) | -4.7 (1.3) | -6.7 (0.5) | -6.4 (1.4) | -6.4 (0.6) | -3.2 (1.3) | -5.3 (0.6) |
| Negative symptom response* | (≥20% improvement of NSFS from baseline) (N) | (10) | (59) | (8) | (63) | (8) | (58) | (8) | (58) |
| Patients meeting response criterion, % | 30 | 47 | 63 | 65 | 63 | 59 | 0 | 52 |
| CGI-I negative symptoms, % (N)* | (10) | (59) | (8) | (63) | (8) | (58) | (8) | (58) |
| Very much improved | 10 | 2 | 0 | 3 | 0 | 9 | 0 | 2 |
| Much improved | 10 | 19 | 50 | 32 | 50 | 31 | 0 | 31 |
| Minimally improved | 30 | 47 | 25 | 48 | 13 | 38 | 63 | 29 |
| No change | 50 | 32 | 25 | 17 | 38 | 21 | 25 | 38 |
| Minimally worse | 0 | 0 | 0 | 0 | 0 | 2 | 13 | 0 |
| PSP total score (N)* | (10) | (59) | (8) | (63) | (8) | (58) | (8) | (58) |
| Change from baseline at wk 8 (SE) | 5.7 (2.6) | 6.5 (1.2) | 10.3 (2.9) | 8.6 (1.1) | 5.8 (2.9) | 7.8 (1.2) | 3.4 (2.9) | 7.8 (1.2) |
| PANSS positive symptom factor score (N) | (10) | (67) | (10) | (71) | (9) | (68) | (9) | (68) |
| Change from baseline at wk 8 (SE) | 0.1 (0.9) | -1.4 (0.4) | -0.5 (1.0) | -1.9 (0.4) | -2.3 (1.0) | -1.0 (0.4) | -1.5 (1.0) | -1.3 (0.4) |
| PANSS disorganized thought/cognition factor score (N) | (10) | (67) | (10) | (71) | (9) | (68) | (9) | (68) |
| Change from baseline at wk 8 (SE) | -1.2 (0.9) | -3.5 (0.4) | -1.4 (0.9) | -4.0 (0.4) | -3.3 (1.0) | -4.0 (0.4) | -1.7 (1.0) | -3.4 (0.4) |
| PANSS total score (N) | (10) | (67) | (10) | (71) | (9) | (68) | (9) | (68) |
| Change from baseline at wk 8 (SE) | -3.8 (3.2) | -11.9 (1.5) | -7.3 (3.4) | -13.9 (1.4) | -14.0 (3.6) | -13.3 (1.5) | -7.7 (3.5) | -11.0 (1.5) |

*observed case at week 8. CGI-I: Clinical Global Impression of Improvement, J: Japanese, N-J: non-Japanese, PANSS: Positive and Negative Syndrome Scale, NSFS: negative symptom factor score, PSP: Personal and Social Performance scale, SE: standard error, wk: week.
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Figure 2. Positive and Negative Syndrome Scale negative symptom factor score response rates at week 8 (intent-to-treat population).

Figure 3. Change in Positive and Negative Syndrome Scale (PANSS) negative symptom factor score from baseline [intent-to-treat population; mean (standard error)].

Figure 4. Differences from placebo and effect sizes of Positive and Negative Syndrome Scale negative symptom factor score change from baseline at week 8 (intent-to-treat population) based on mixed-model repeated-measure analysis.
-3.2 in the placebo and 60-mg groups, respectively) or non-Japanese patients (-5.5 and -5.3 in the placebo and 60-mg groups, respectively), which was in congruence with the results of the original study (Table 2). In Japanese patients, the response to placebo was lower than in non-Japanese patients, and there was a trend toward a greater difference in the change in personal and social performance scale score from baseline at week 8 (intent-to-treat population).

![Figure 5](image-url)

**Figure 5.** Change in Personal and Social Performance Scale score from baseline at week 8 (intent-to-treat population). Changes were compared using analysis of covariance, as described in the original paper.12

![Figure 6](image-url)

**Figure 6.** Change in Clinical Global Impression-Globally Improvement negative symptoms at week 8 (intent-to-treat population).

| Table 3. Correlation between personal and social performance total score and PANSS factor scores at baseline (ITT population) |
|---------------------------------------------------------------|
| **Positive and Negative Syndrome Scale factor scores**       | **Total** | **Japanese** | **Non-Japanese** |
|                                                              | Correlation with PSP total score | R² | Correlation with PSP total score | R² | Correlation with PSP total score | R² |
| Anxiety/depression                                          | -0.0174 | 0.0003 | -0.0763 | 0.0058 | 0.0285 | 0.0008 |
| Disorganized thought/cognition                               | -0.1520 | 0.0231 | -0.1440 | 0.0207 | -0.1866 | 0.0348 |
| Uncontrolled hostility/excitement                            | -0.1194 | 0.0143 | -0.0795 | 0.0063 | -0.1036 | 0.0107 |
| Negative symptom                                            | -0.3725 | 0.1387 | -0.4089 | 0.1672 | -0.3473 | 0.1206 |
| Positive symptom                                            | -0.1373 | 0.0189 | -0.2174 | 0.0473 | -0.0887 | 0.0079 |

Data are shown as correlation coefficients (R) and R². PSP: personal and social performance.
in PANSS factor scores between the placebo group and the 10-mg and 30-mg groups, in particular for the 30-mg group (Figure 3, Table 2). In the 10-mg and 30-mg groups, the effect sizes (the mean difference divided by the common standard deviation) for the change in NSFS were -0.60 and -1.02, respectively, among Japanese patients, and -0.25 and -0.19, respectively, among non-Japanese patients (Figure 4).

The PSP score improved at week 8 in both Japanese and non-Japanese patients, while baseline PSP scores were generally lower in Japanese than non-Japanese patients (Figure 5, Table 2).

The response rate (“Very much improved” and “Much im-

Table 4. Number of patients with at least one AE and SAE (safety population)

|               | Placebo | 10 mg/day | 30 mg/day | 60 mg/day |
|---------------|---------|-----------|-----------|-----------|
| Safety population | N=80    | N=82      | N=81      | N=78      |
| Japanese      | N=10    | N=10      | N=9       | N=9       |
| Non-Japanese  | N=70    | N=72      | N=72      | N=69      |
| AEs: total, N (%) | 32 (40) | 34 (41)   | 33 (41)   | 36 (46)   |
| Japanese, N (%) | 8 (80)  | 7 (70)    | 4 (44)    | 4 (44)    |
| Non-Japanese, N (%) | 24 (34) | 27 (38)   | 29 (40)   | 32 (46)   |
| AEs (treatment-related): total, N (%) | 16 (20) | 15 (18)   | 19 (23)   | 24 (31)   |
| Japanese, N (%) | 2 (20)  | 4 (40)    | 4 (44)    | 2 (22)    |
| Non-Japanese, N (%) | 14 (20) | 11 (15)   | 15 (21)   | 22 (32)   |
| SAEs: total, N (%) | 0 (0)   | 1 (1)     | 2 (2)     | 3 (4)     |
| Japanese, N (%) | 0 (0)   | 1 (10)    | 0 (0)     | 0 (0)     |
| Non-Japanese, N (%) | 0 (0)   | 0 (0)     | 2 (3)     | 3 (4)     |
| SAEs (treatment-related): total, N (%) | 0 (0)   | 1 (1)     | 1 (1)     | 1 (1)     |
| Japanese, N (%) | 0 (0)   | 1 (10)    | 0 (0)     | 0 (0)     |
| Non-Japanese, N (%) | 0 (0)   | 0 (0)     | 1 (1)     | 1 (1)     |

AEs: adverse events, SAEs: serious adverse events, N: number of patients

Table 5. Adverse events occurring at an incidence of 5% or more in the total population (safety population)

|               | Placebo | 10 mg/day | 30 mg/day | 60 mg/day |
|---------------|---------|-----------|-----------|-----------|
| Safety population | N=80    | N=82      | N=81      | N=78      |
| Japanese      | N=10    | N=10      | N=9       | N=9       |
| Non-Japanese  | N=70    | N=72      | N=72      | N=69      |
| Somnolence: total, N (%) | 2 (3)   | 6 (7)     | 4 (5)     | 8 (10)    |
| Japanese, N (%) | 0 (0)   | 2 (20)    | 1 (11)    | 2 (22)    |
| Non-Japanese, N (%) | 2 (3)   | 4 (6)     | 3 (4)     | 6 (9)     |
| Dizziness: total, N (%) | 2 (3)   | 1 (1)     | 3 (4)     | 9 (12)    |
| Japanese, N (%) | 2 (20)  | 1 (10)    | 2 (22)    | 1 (11)    |
| Non-Japanese, N (%) | 0 (0)   | 0 (0)     | 1 (1)     | 8 (12)    |
| Headache: total, N (%) | 1 (1)   | 2 (2)     | 2 (2)     | 7 (9)     |
| Japanese, N (%) | 0 (0)   | 0 (0)     | 1 (11)    | 1 (11)    |
| Non-Japanese, N (%) | 1 (1)   | 2 (3)     | 1 (1)     | 6 (9)     |
| Nasopharyngitis: total, N (%) | 6 (8)   | 4 (5)     | 0 (0)     | 2 (3)     |
| Japanese, N (%) | 3 (30)  | 2 (20)    | 0 (0)     | 1 (11)    |
| Non-Japanese, N (%) | 3 (4)   | 2 (3)     | 0 (0)     | 1 (1)     |

N: number of patients
proved”) in CGI-I negative symptoms score at week 8 (Figure 6, Table 2) was greater in the 10-mg and 30-mg groups than in the placebo group, in Japanese and non-Japanese patients.

In a post-hoc analysis, the correlations between the PSP total score and the score for each PANSS symptom factor at baseline were examined. The strongest correlations were between the PSP score and the PANSS negative symptom factor score, in both Japanese and non-Japanese patient populations (Japanese: correlation coefficient=-0.41; non-Japanese: correlation coefficient=-0.35) (Table 3).

**Safety**

There were no major differences in safety profiles between Japanese and non-Japanese patients (Table 4 and 5). The most common adverse event in Japanese patients was “dizziness” and “Nasopharyngitis.” The incidence rates of “somnolence,” “dizziness,” and “headache” were higher in the 60-mg group in non-Japanese patients, but this trend was not observed in Japanese patients (Table 5). “Anxiety” in one patient in the 10-mg group was the only serious adverse event observed among Japanese patients (data not shown).

Dose-dependent changes in the mean blood hemoglobin concentration were observed in Japanese and non-Japanese patients. Decrease of >2.0 g/dL in hemoglobin was seen in 4 to 22% of the non-Japanese patients; however, only one Japanese patient was reported in the 60-mg group (Table 6). Otherwise, no clinically significant changes were observed in vital signs, electrocardiograms, or extrapyramidal symptoms (BAS, SAS, and AIMS) in the safety analysis population. No other particular concerns were observed in Japanese patients.

**DISCUSSION**

This clinical trial was a proof-of-concept study designed to assess the efficacy of bitopertin on negative symptoms of schizophrenia in clinical settings. In this study conducted in ten countries, including Japan, a significant improvement in PANSS NSFS, the primary endpoint, was observed in the per-protocol population. The safety profile of bitopertin was also confirmed in patients with schizophrenia. Furthermore, in this study, a similar profile was observed in the Japanese patients treated with bitopertin 10 and 30 mg; the 60-mg dose was essentially ineffective for improving PANSS NSFS.

Although baseline PSP scores were lower among Japanese patients, there were no differences between Japanese and non-Japanese patients in terms of demographic characteristics and baseline symptom scores on the PANSS and CGI. Social acceptance of patients with schizophrenia has been reported to be lower in Japan than in the US and Australia. According to the PSP, which assesses the severity of impairment of personal and social functioning based on information from caregivers, prejudice toward patients with schizophrenia may be a contributing factor to the lower rating in Japanese patients among those with similar severity of symptoms. Examination of differences between Japanese and non-Japanese patients in each PSP domain revealed that the personal and social functioning tended to be rated lower on average in the Japanese population in all domains of “Socially useful activities,” “Personal and social relationships,” “Self-care,” and “Disturbing and aggressive behaviors” (data not shown). Despite the difference in the baseline, changes in PSP were similar between Japanese and non-Japanese patients.

Although differences were observed in the type of antipsychotic drugs and concomitant use rate of benzodiazepine between Japanese and non-Japanese patients, these did not significantly affect the efficacy and safety evaluations. Risperidone-related products were found to be the most commonly used concomitant drugs in both Japanese and non-Japanese patients. Olanzapine and aripiprazole were also commonly used in both Japanese and non-Japanese patients. However, olanzapine was much more commonly used among non-Japanese patients (29% vs. 18%), and aripiprazole was much more commonly used among Japanese patients (24% vs. 9%). The World Federation of Societies of Biological Psychiatry Guidelines for Treatment of Schizophrenia recommends olanzapine and amisulpride for the treatment of primary negative symptoms.

| Table 6. Number of patients with a decrease in hemoglobin (>2.0 g/dL) from baseline (safety population) |
|---------------------------------------------------------------|
| Bitopertin | Placebo | 10 mg/day | 30 mg/day | 60 mg/day |
| Safety population | N=80 | N=82 | N=81 | N=78 |
| Japanese | N=10 | N=10 | N=9 | N=9 |
| Non-Japanese | N=70 | N=72 | N=72 | N=69 |
| Hemoglobin decreased (>2.0 g/dL); total, N (%) | 3 (4) | 4 (5) | 8 (10) | 16 (21) |
| Japanese, N (%) | 0 (0) | 0 (0) | 0 (0) | 1 (11) |
| Non-Japanese, N (%) | 3 (4) | 4 (6) | 8 (11) | 15 (22) |

N: number of patients
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A meta-analysis conducted by Leucht et al. has shown that aripiprazole is the best tolerated and has the least sedative effects among the atypical antipsychotics allowed as concomitant baseline medications in the present study (risperidone, olanzapine, quetiapine, and aripiprazole). The common use of aripiprazole in the Japanese patient population may be a reflection of prescription practices that put emphasis on the tolerability in chronic patients rather than the treatment of primary negative symptoms. The difference between Japanese and non-Japanese patients in the proportion of patients receiving a benzodiazepine concomitantly in the present study appears to reflect the general trend of prescription use for patients with schizophrenia in Japan.

In the present study, the placebo response was lower in Japanese patients than in non-Japanese patients. Similar trends were observed in clinical trials on another antipsychotic drug for schizophrenia. In the original paper, the authors suggested the improvement observed in the placebo group may be attributed to the intense interaction and intimate communication between the patients and the study staff in a clinical trial setting. In Japan, patients enrolled in clinical studies are mostly those cared for by clinical investigators. Therefore, there are no major differences between the routine clinical practice and that during participation in a clinical study. This may explain the small placebo response in this study.

A meta-analysis of placebo-controlled studies of antipsychotic drugs conducted from 1970 onwards found a gradual increase in placebo response in the past 2–30 years. The authors suggested this increase could be explained by an increase in the number of study sites per study and a decrease in the percentage of academic sites participating. In the editorial accompanying the meta-analysis, Leucht et al. discuss that nonacademic sites are more motivated by financial incentives; thus, they aim to enroll as many patients as possible. This trend will create greater variation in study results, thereby decreasing differences in efficacy between the active drug and placebo.

There were 13 facilities participating in this study from Japanese hospitals and three national hospitals. This participation provided in all treatment arms, which showed that appropriate communication between the patients and the study staff in a clinical trial setting. In Japan, patients enrolled in clinical studies are mostly those cared for by clinical investigators. Therefore, there are no major differences between the routine clinical practice and that during participation in a clinical study. This may explain the small placebo response in this study.

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**Conflicts of Interest**

YH has served as a clinical trial advisor for Otsuka Pharmaceutical Co., Ltd. and Chugai Pharmaceutical Co., Ltd.; has served on an advisory board for Mochida Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Eli Lilly Japan K.K., Chugai Pharmaceutical Co., Ltd., and Janssen Pharmaceutical K.K.; has received research grant from Otsuka Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K.K., Pfizer Japan Inc., Sanofi K.K., Astellas Pharma Inc., and Sumitomo Dainippon Pharma Co., Ltd.; has received a lecture honorarium from Otsuka Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Eli Lilly Japan K.K., Sumitomo Dainippon Pharma Co., Ltd., GlaxoSmithKline K.K., Astellas Pharma Inc., MSD K.K., Asahi Kasei Pharma Corporation, Ono Pharmaceutical Co., Ltd., Yoshitomiyakukin Corporation, and Eisai Co., Ltd.

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