Use of the Functioning Assessment Short Test (FAST) in defining functional recovery in bipolar I disorder. Post-hoc analyses of long-term studies of aripiprazole once monthly as maintenance treatment

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Purpose: There is growing agreement that definitions of “recovery” in bipolar-I disorder (BP-I) should include functional outcomes beyond sustained symptomatic remission. In this post-hoc analysis, we assessed functional recovery rates according to the validated Functioning Assessment Short Test (FAST) in participants with BP-I after 52 weeks of maintenance treatment with aripiprazole once monthly (AOM).

Patients and methods: Rates of functional recovery with AOM 400 were investigated in two 52-week studies. NCT01567527 was a placebo-controlled, double-blind, randomized-withdrawal study and NCT01710709 was an open-label study. Functional recovery, assessed at the end of the respective maintenance phases, was defined as a total FAST score of \( \leq 11 \) for 8 consecutive weeks.

Results: Post-hoc analyses included 229 patients from the randomized-withdrawal study (AOM 400 n=116; placebo n=113). The open-label study included 402 patients (including 321 de novo patients and 81 rollover patients who had completed the randomized-withdrawal study). In the randomized-withdrawal study, functional recovery was achieved by 30.2% (n=35) of the AOM 400 group compared with 24.8% (n=28) in the placebo group. The difference was not statistically significant (\( p=0.39 \)). In the open-label study, 36% (n=116) of de novo patients and 43% (n=35) of rollover patients had functionally recovered after 52 weeks of AOM 400 treatment.

Conclusion: These data highlight the utility of a sustained FAST total score of \( \leq 11 \) as a definition of recovery and emphasize the possibility of achieving this ambitious treatment goal with effective long-term treatment.

Keywords: bipolar disorder, aripiprazole, long-acting injectable, maintenance, functioning, recovery

Plain language summary

Functional recovery is beginning to be considered equally as important as symptomatic recovery in patients with bipolar I disorder (BP-I). We present post-hoc analyses of two studies in which we assessed functional recovery rates according to the validated Functioning Assessment Short Test (FAST) in participants with BP-I after 52 weeks of maintenance treatment with aripiprazole 400 mg once monthly (AOM). To our knowledge, this is the first analysis of clinical trials to use the FAST scale as a definition of functional recovery, and we show that 30–43% of patients achieved functional recovery after 52 weeks’ maintenance treatment with AOM.
Introduction
While many people living with bipolar disorders regain psychosocial functioning upon symptomatic remission, the majority suffer persistent functional difficulties, often despite adequate control of their core affective symptoms. Such functional deficits include problems in their ability to work, study, live independently, maintain interpersonal relationships and participate in recreational activities. Mood stabilizers and/or atypical antipsychotics are well accepted as the mainstays of bipolar-I disorder (BP-I) treatment. Compared with their oral counterparts, long-acting injectable (LAI) atypical antipsychotic formulations allow for better adherence with more consistent dosing and have recently shown to be more effective in preventing hospitalization of BP-I patients due to mental or physical illness. Aripiprazole 400 mg once monthly (AOM 400) is an LAI approved by the US Food and Drug Administration as maintenance monotherapy treatment for BP-I. Results from recent placebo-controlled and open-label studies show that maintenance treatment with AOM 400 delays the time to mood episode recurrence and is safe and well-tolerated.

There is growing agreement that definitions of “functional recovery” in bipolar disorders should include functional outcomes beyond sustained symptomatic remission. Both studies of AOM 400 as maintenance treatment used the Functioning Assessment Short Test (FAST), which was developed as a short simple interview-administered instrument for use in patients with psychiatric disorders, and especially bipolar disorders. The FAST has been shown to have strong psychometric properties and is able to detect differences between euthymic and acute patients with bipolar disorder. We have previously reported maintenance of improvement in FAST scores over 52 weeks in the AOM group of the placebo-controlled study. Taking into account the FAST cut off scores proposed by Rosa et al, we defined recovery as a FAST total score ≤11 for ≥8 consecutive weeks and assessed the rates of functional recovery in participants with BP-I after long-term (52-week) treatment with AOM 400.

Materials and methods
The efficacy and safety of AOM 400, given every 4 weeks, as maintenance treatment of BP-I was investigated in two, 52-week studies, the full methodologic details of which have been previously published:

1. A placebo-controlled, double-blind, randomized-withdrawal study (NCT01567527) conducted in 103 sites in 7 countries.
2. An open-label, multicenter study (NCT01710709) conducted in 149 sites in 10 countries.

Both studies were conducted in compliance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines for conducting, recording and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent had been obtained from them. The informed consent form, protocol and amendments for this trial were submitted to and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each respective trial site or country (Table S1).

Study design
Study designs are summarized in Figure 1. Briefly, in the randomized-withdrawal study, participants completed oral aripiprazole conversion and stabilization phases if needed, followed by a single-blind AOM 400 stabilization phase. Those meeting stability criteria (outpatient status, Young Mania Rating Scale [YMRS] total score ≤12, Montgomery–Asberg Depression Rating Scale [MADRS] total score ≤12 and no active suicidality) were randomized to double-blind treatment with AOM 400 or placebo for 52 weeks.

The open-label study had two protocols, depending on whether the participants were de novo or had rolled-over from the randomized-withdrawal study. Whereas rollover participants began the 52-week, open-label AOM 400 maintenance phase immediately after completing the prior double-blind maintenance phase (AOM 400 or placebo), de novo participants entered a 4- to 12-week oral aripiprazole stabilization phase before entering the open-label maintenance phase. If de novo participants were receiving a non aripiprazole antipsychotic medication before enrollment, a 4- to 6-week oral aripiprazole cross-titration phase was implemented before the oral aripiprazole stabilization phase.

Participants
Both studies enrolled outpatients (18–65 years) who had a clinical diagnosis of BP-I (DSM, 1994), and who were further verified by the Mini-International Neuropsychiatric Interview.
Participants included in the open-label study were rolled over from the double-blind study or were AOM 400 treatment-naive and enrolled de novo.

All participants in the randomized-withdrawal study and new participants recruited to the open-label study were eligible for the trial if they had experienced ≥1 previous manic or mixed episode with manic symptoms of sufficient severity to require hospitalization, treatment with a mood stabilizer, or treatment with an antipsychotic agent. Study entry criteria were similar, except that the randomized-withdrawal study required participants to have a YMRS score ≥20 and excluded participants with a mixed or depressive episode, and the open-label study had no YMRS criterion and only excluded participants with a depressive episode. The open-label study also included rollover participants, who had completed the maintenance phase of the randomized-withdrawal study (AOM 400 or placebo) without recurrence of a mood episode. Participants previously on placebo had prior exposure to AOM 400 due to the 12- to 28-week AOM 400 stabilization phase.

Analysis of functional recovery
These analyses included all participants (both studies) who received maintenance study treatment and had ≥1 post baseline FAST assessment. Functioning was assessed using the FAST (Table S2), where trained investigators ranked the participant’s level of difficulty from 0 (no difficulty) to 3 (severe difficulty). Domains are based on grouping of the 24 individual items: autonomy (4 items), occupational functioning (5 items), cognitive functioning (5 items), financial issues (2 items), interpersonal relationships (6 items) and leisure time (2 items). The FAST total score (range: 0–72) is calculated as the sum of each of the 24 item scores, with higher scores representing worse function. Any one missing score led to a missing total score. In addition, our definition included a minimum duration of 8 consecutive weeks to ensure that transient fluctuations were not designated as recovery.

Functional recovery was thus defined post-hoc as a FAST total score of ≤11 for 8 consecutive weeks. FAST total and domain scores (LOCF) were summarized at baseline and Week 52 of the respective maintenance phases using mean and SD for 1) all participants included in the analyses of FAST data and 2) those participants who met criteria for functional recovery. Between-group differences were derived from an ANOVA model with treatment and region as baseline factors.

Results
Patient disposition and baseline characteristics
Of the 266 participants entered into the randomized-withdrawal phase of the placebo-controlled study, 116 received AOM 400 and 113 received placebo and had
≥1 post-baseline FAST assessment. In the open-label study, 402 of the original 464 participants entering the maintenance phase had ≥1 post baseline FAST assessment (321 de novo participants, 81 rollover participants). Overall 52/81 of the rollover participants had already received treatment with AOM 400 for up to 52 weeks at baseline in the placebo-controlled, double-blind study (for these participants total treatment duration, therefore, ranged between 52 and 80 weeks).

Baseline characteristics for the full populations of the two studies have been previously published. In brief, 57.5% of participants (n=266) in the randomized-withdrawal study were female, the mean±SD age was 40.6 ± 11.0 years and age at first manic episode was 25.0 ± 10.1 years; participants had 3.5 ± 4.0 prior hospitalizations for a mood episode. The mean YMRS total score was 2.8 ± 3.3, MADRS score was 2.7 ± 3.4 and FAST score was 15.4 ± 12.7 (Phase D baseline). For the open-label study, 57.8% of participants (n=464) were female, the mean age was 41.1 ± 11.8 years and age at first BP-I diagnosis was 29.1 ± 11.7 years. The mean YMRS total score was 2.3 ± 2.9 and MADRS score was 3.2 ± 3.2.

Rates of functional recovery
During the maintenance phase of the placebo-controlled, double-blind study, 30.2% of participants (35/116) receiving AOM 400 and 24.8% of participants (28/113) receiving placebo achieved FAST recovery. Recovery rates were not statistically significant between AOM 400 and placebo groups (p=0.3944 [Cochrane–Mantel–Haenszel General Association Test Controlling Region]). Of the participants who met recovery criteria in the double-blind phase, 33 (n=23 previously treated with AOM 400 and n=10 previously treated with placebo) agreed to “roll-over” into the subsequent open-label study.

In the open-label study, functional recovery as measured by FAST after 52 weeks of treatment was achieved by 36% of de novo participants (n=116) (Figure 2). Overall, 43% of rollover participants (35/81) met the criteria for functional recovery. This included 20 participants who had previously received AOM 400 and met criteria for functional recovery in the double-blind study and who remained recovered after completing the following open-label study (ie, they remained recovered into their second year). An additional 5 participants had not met criteria for functional recovery with AOM 400 during the placebo-controlled study but achieved functional recovery in the open-label study, while 3 participants were considered to meet functional recovery criteria in the placebo-controlled study but not in the open-label study. Of the participants previously on placebo, 10 met criteria for functional recovery with open-label AOM 400, including 8 who met criteria for recovery in both studies.

**FAST scores**
In the randomized-withdrawal study, FAST total scores were generally maintained in the group of participants who received AOM 400 (mean±SD score of 15.92 ± 13.19 at baseline and 16.59±13.98 at last visit) and were worsened in the placebo group (14.82 ± 12.12 at baseline and 20.91 ± 16.87 at Week 52). The mean [95% CI] treatment effect (AOM 400 vs placebo) of −3.98 [−7.52,
participants showed that mean FAST total scores numerically improved from 5.47 ± 5.50 at baseline to 3.51 ± 3.62 at Week 52 in the AOM 400 group and from 4.44 ± 4.23 at baseline to 2.75 ± 2.86 at Week 52 in the placebo group. Analyses by domain are provided in Table 1.

In the open-label study, de novo participants significantly improved from a mean of 17.90 ± 13.51 at baseline to 14.02 ± 12.02 at the end of the 4- to 12-week stabilization phase (p<0.00001, one-sided Z test). FAST total scores were then maintained during the 52-week maintenance phase (from 14.02 ± 12.02 to 13.98 ± 13.05 in de novo participants and from 12.89 ± 12.22 to 13.95 ± 13.46 in rollover participants). For those participants who met criteria for functional recovery, mean FAST total scores (baseline of maintenance phase/Week 52) were 4.09 ± 4.00/3.59 ± 3.39 in the de novo group and 3.71 ± 3.00/3.54 ± 3.35 in the rollover group.

Discussion
To the best of our knowledge, this is the first analysis of clinical trials to use FAST thresholds as a definition of functional recovery and highlight the scale’s utility in understanding the effectiveness of an intervention. Our analyses of two long-term studies demonstrate that maintenance treatment with AOM 400 can help patients living with BP-I achieve long-term functional recovery. Overall, 30–43% of participants who received AOM 400 for at least 52 weeks achieved long-term functional recovery as determined by a FAST score of ≤11 for at least 8 consecutive weeks.

Although the threshold for recovery used in these analyses was initially based on the FAST validation studies, which found that a score of >11 offers the best discriminant sensitivity and specificity, more recent studies support its use as a relatively conservative definition. According to Bonnin et al, euthymic BP-I outpatients in this category “present good functioning in all areas, they live independently, they work and they have a meaningful social engagement”. In terms of recovery rates, our exploratory analyses of the randomized-withdrawal study did not show statistical separation from placebo. This is likely due, in part, to a survivor effect of the study design, where participants who initially had marked functional improvement and then stabilization (over 12–28 weeks) were able to remain functionally recovered, even when later randomized to placebo. Nevertheless, as previously reported, participants randomized to placebo showed a significant worsening in FAST scores relative to AOM and a higher risk of relapse.

Overall, at least 57% of the participants who met criteria for functional recovery with AOM 400 maintenance treatment during the placebo-controlled study (and 87% of those who also chose to “roll over” to open-label treatment) remained recovered after completing the subsequent open-label study (ie, after 2 years of stable treatment). Of note, a small proportion of participants did not meet functional recovery criteria with active maintenance treatment during the first year, but did during the second year, thus supporting the idea that functional recovery takes longer to achieve than symptom recovery. Here, it is important to acknowledge that the entire rollover subgroup was highly enriched for patients who responded to and tolerated AOM treatment (during the stabilization phase for placebo patients and during the stabilization plus maintenance phases for AOM 400 patients). Indeed, due to the enriched discontinuation study designs, the generalizability of all results presented herein is limited to patients experiencing a manic episode and stabilized on AOM 400.

In terms of the maintenance effect (in both studies), there were only small changes in domain scores, with all functional domains remaining relatively stable with AOM 400 treatment. Likewise, all FAST domains appeared to remain similarly stable in the subgroup of participants who had functionally recovered. Subgroup analyses of the functionally “recovered” participants showed that mean FAST total scores were already <6 at baseline of the maintenance phase, which is similar to a control group of participants without bipolar disorder (mean of 5.93). The rates of functional recovery seen with long-term AOM treatment are in line with or slightly higher than those previously reported after 52 weeks of olanzapine treatment. However, it should also be noted that the olanzapine study defined functional recovery using a combination of the psychosocial functioning sub scale of the SF-36 and work status and disability support measures – the comparability of which with the validated FAST scale is unknown.

Limitations of this study include the post-hoc nature of the recovery rate analyses and the lack of a blinded comparator in the open-label study. Whereas the minimum duration of 8 consecutive weeks could be considered relatively short, we based our definition to be consistent with the recommendations of the International Society for
Table 1  FAST scores at baseline and Week 52 of each study (LOCF)

|                          | Randomized-withdrawal study | Open-label AOM 400 maintenance study | De novo | Rollover |
|--------------------------|-----------------------------|-------------------------------------|---------|----------|
|                          | AOM 400 | Placebo | Treatment effect (AOM vs placebo); LS mean [95% CI] |          |          |
| **Autonomy score**       |         |         |                                                      |         |          |
| Total population         |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 1.47 (2.07) | 1.35 (2.10) | −0.67 [−1.35,0.02] | 1.23 (1.89) | 1.19 (2.07) |
| Week 52; mean (SD)       | 1.72 (2.49) | 2.43 (3.19) | P=0.055 | 1.19 (1.46) | 1.46 (2.27) |
| Recovery population      |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 0.29 (0.63) | 0.04 (0.19) | 0.01 [−0.23,0.24] | 0.28 (0.79) | 0.26 (0.78) |
| Week 52; mean (SD)       | 0.17 (0.45) | 0.11 (0.42) | P=0.958 | 0.24 (0.60) | 0.34 (0.94) |
| **Occupational functioning score** |         |         |                                                      |         |          |
| Total population         |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 5.73 (4.91) | 5.69 (5.35) | −0.82 [−1.88,0.24] | 4.69 (4.69) | 4.42 (5.18) |
| Week 52; mean (SD)       | 5.29 (4.91) | 6.39 (5.54) | P=0.128 | 4.50 (4.69) | 5.05 (5.26) |
| Recovery population      |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 2.26 (2.74) | 1.56 (1.89) | 0.24 [−0.63,1.11] | 1.15 (1.85) | 0.97 (1.32) |
| Week 52; mean (SD)       | 1.14 (1.65) | 0.93 (1.59) | P=0.582 | 1.04 (1.83) | 0.91 (1.38) |
| **Cognitive functioning score** |         |         |                                                      |         |          |
| Total population         |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 3.28 (3.38) | 2.91 (3.18) | −0.56 [−1.44,0.32] | 2.97 (2.99) | 2.69 (3.20) |
| Week 52; mean (SD)       | 3.64 (3.62) | 4.21 (4.06) | P=0.212 | 2.00 (3.14) | 2.86 (3.42) |
| Recovery population      |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 0.97 (1.57) | 0.96 (1.29) | 0.32 [−0.12,0.76] | 1.14 (1.38) | 0.97 (1.67) |
| Week 52; mean (SD)       | 0.66 (1.21) | 0.29 (0.66) | P=0.155 | 0.96 (1.42) | 0.86 (1.50) |
| **Financial issues score** |         |         |                                                      |         |          |
| Total population         |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 1.20 (1.66) | 1.17 (1.48) | −0.35 [−0.74,0.04] | 1.17 (1.59) | 0.93 (1.40) |
| Week 52; mean (SD)       | 1.16 (1.53) | 1.57 (1.72) | P=0.075 | 1.09 (1.58) | 1.09 (1.49) |
| Recovery population      |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 0.32 (0.68) | 0.57 (1.23) | −0.06 [−0.49,0.36] | 0.40 (0.90) | 0.31 (0.76) |
| Week 52; mean (SD)       | 0.29 (0.83) | 0.43 (0.88) | P=0.777 | 0.41 (0.95) | 0.31 (0.76) |
| **Interpersonal relationships score** |         |         |                                                      |         |          |
| Total population         |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 2.84 (3.50) | 2.45 (2.87) | −1.32 [−2.32,−0.31] | 2.75 (3.33) | 2.52 (3.38) |
| Week 52; mean (SD)       | 3.15 (3.82) | 4.50 (4.67) | P=0.011 | 2.71 (3.63) | 2.33 (3.62) |
| Recovery population      |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 1.15 (1.62) | 0.71 (1.01) | 0.17 [−0.37,0.70] | 0.67 (1.09) | 0.66 (1.21) |
| Week 52; mean (SD)       | 0.77 (1.26) | 0.46 (0.79) | P=0.537 | 0.50 (1.01) | 0.63 (1.03) |
| **Leisure time score**   |         |         |                                                      |         |          |
| Total population         |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 1.40 (1.57) | 1.18 (1.28) | −0.19 [−0.58,0.20] | 1.27 (1.44) | 1.14 (1.40) |
| Week 52; mean (SD)       | 1.62 (1.65) | 1.81 (1.76) | P=0.339 | 1.45 (1.62) | 1.16 (1.45) |
| Recovery population      |         |         |                                                      |         |          |
| Baseline; mean (SD)      | 0.47 (1.08) | 0.50 (0.64) | −0.00 [−0.38,0.38] | 0.46 (0.78) | 0.54 (0.89) |
| Week 52; mean (SD)       | 0.49 (0.92) | 0.54 (0.69) | P=0.992 | 0.44 (0.86) | 0.49 (0.82) |
Bipolar Disorders for symptomatic recovery.\textsuperscript{12} While LOCF analyses can be criticized, we used the same methods of imputation as per the primary study analyses.\textsuperscript{7,8} Although the roll over group provided important insights into the longevity and time course of functional recovery, it is important that almost half (47.6\%) of the participants who met criteria for functional recovery in the double-blind phase did not choose to “roll over” to the open-label trial. Finally, it has been recently suggested that euthymic patients can be categorized into three main functional types, low-, intermediate- and high-functioning, and that the low- and intermediate-functioning types have higher subthreshold depressive/manic symptoms and worse cognition, particularly in terms of processing speed.\textsuperscript{17} Future studies including patients with depression as well as cognitive assessments may lend further clarity to the predictors of long-term functional recovery with AOM 400.

**Conclusion**

Functional recovery is beginning to be considered equally as important as symptomatic recovery, since key goals for patients and relatives are to fulfill role expectations at work/school and home and to maintain good relationships.\textsuperscript{18–20} Almost all individuals with bipolar disorders require maintenance treatment to prevent subsequent episodes, reduce residual symptoms and restore functioning.\textsuperscript{4} The results of this study demonstrate the utility of a FAST total score of $\leq$11 for 8 consecutive weeks as a definition of functional recovery in BP-I and highlight the possibility of achieving this ambitious treatment goal with effective treatment.

**Ethics approval and informed consent**

Both studies were conducted in compliance with the International Conference of Harmonization and Good Clinical Practice consolidated guideline.\textsuperscript{7,8} Protocols were approved by an institutional review board or independent ethics committee, as appropriate. Informed consent was obtained from all participants or their legal representatives as necessary.

**Abbreviations**

AOM, aripiprazole once monthly; BP-I, bipolar I disorder; FAST, Functioning Assessment Short Test; LAI, long-acting injectable; MADRS, Montgomery–Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

**Data sharing statement**

Otsuka and H. Lundbeck are committed to sharing data in accordance with the European Federation of Pharmaceutical Industries and Associations (EFPIA)/Pharmaceutical Research and Manufacturers of America (PhRMA) principles for responsible sharing of clinical trial data guidelines and as required by applicable legislation. Legitimate research requests will be considered. For inquiries on availability of data of interest, researchers should contact Otsuka (DT-inquiry@otsuka.jp). Please visit [https://clinical-trials.otsuka.com/For-Researchers.aspx](https://clinical-trials.otsuka.com/For-Researchers.aspx) for further details.

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**Author contributions**

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

**Disclosure**

Jessica Madera, Peter Zhang and Ross A Baker are employed by Otsuka Pharmaceutical Development and Commercialization Inc. Pedro Such is employed by H. Lundbeck A/S. Iria Grande reports consultancy for Otsuka Pharmaceutical Development and Commercialization Inc. and H. Lundbeck A/S. Iria Grande also reports grants, personal fees, and non-financial support from the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III. She received personal fees from AstraZeneca, Ferrer, Janssen Cilag, H. Lundbeck, and Lundbeck-Otsuka, during the conduct of the study and outside the submitted work. The authors report no other conflicts of interest in this work.
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Supplementary materials

Table S1 The Functioning Assessment Short Test (FAST)

| Physician rates each item according to difficulty: |  |
|---------------------------------------------------|---|
| (0) None (1) mild (2) moderate (3) severe        |  |

| AUTONOMY                                           | FINANCIAL ISSUES |
|---------------------------------------------------|------------------|
| 1. Taking responsibility for a household          | 15. Managing your own money |
| 2. Living on your own                             | 16. Spending money in a balanced way |
| 3. Doing shopping                                |                  |
| 4. Taking care of yourself (physical aspects, hygiene) |                  |

| OCCUPATIONAL FUNCTIONING                          | INTERPERSONAL RELATIONSHIPS |
|---------------------------------------------------|-----------------------------|
| 5. Holding down a paid job                        | 17. Maintaining a friendship or friendships |
| 6. Accomplishing tasks as quickly as necessary    | 18. Participating in social activities |
| 7. Working in the field in which you were educated| 19. Having good relationships with people close to you |
| 8. Occupational earnings                          | 20. Living together with your family |
| 9. Managing the expected workload                 | 21. Having satisfactory sexual relationships |

| COGNITIVE FUNCTIONING                              | LEISURE TIME |
|---------------------------------------------------|--------------|
| 10. Ability to concentrate on a book, film        | 23. Doing exercise or participating in sport |
| 11. Ability to make mental calculations           | 24. Having hobbies or personal interests |
| 12. Ability to solve a problem adequately         |              |
| 13. Ability to remember newly-learned names       |              |
| 14. Ability to learn new information              |              |

Note: Data from Rosa et al (2007).\(^{10}\)
| Local or central IRB/ IEC | IRB/IEC Name                                                                 |
|--------------------------|-----------------------------------------------------------------------------|
| Central IRB - Canada     | Schulman Associates Institutional Review Board, 4445 Lake Forest Drive, Suite 300, Cincinnati, Ohio 45242 |
| Local IRB - Japan        | Yuge Hospital Institutional Review Board, 679-2 Yuge, Tatsuda-machi, Kita-ku, Kumamoto prefecture 861-8002, Japan |
|                          | Arakaki Hospital Institutional Review Board, 4-10-3 Ageda, Okinawa, 904-0012, Japan |
|                          | South Toyama Nakagawa Institutional Review Board 146 Omachi, Toyama city, Toyama prefecture, 939-8073, Japan |
|                          | NHO Tottori Medical Center Institutional Review Board 876 Mitsu, NHO Tottori Medical Center, Tottori city, Tottori prefecture, 689-0203, Japan |
|                          | Goryokai Medical Corporation Institutional Review Board 6-2-3 9-jo, Shinoro, Kita-ku, Sapporo city 002-8029, Hokkaido, Japan |
|                          | Asai Clinic Institutional Review Board, 1-14 Katabira-cho, Hodogaya-ku, Yokohama 240-0013, Kanagawa, Japan |
|                          | Asakayama General Hospital Institutional Review Board 3-3-16 Imaike-cho, Sakai-ku, Sakai city 590-0018, Osaka, Japan |
|                          | Japan Nara Medical University Masatoshi Hasegawa, 840 Shijo-cho, Kashihara 634-8522, Nara, Japan |
|                          | Hoshi General Hospital Institutional Review Board 159-1 Mukaikawara-machi, Koriyama 963-8501, Fukushima, Japan |
|                          | Shinagawa East One Medical Clinic Institutional Review Board 2-16-1, Konan Minato-ku, Tokyo 108-0075, Japan |
|                          | Seiwakai Medical Corporation Association Yutaka Clinic Institutional Review Board 3-14-20 Sagamiono, Minami-ku, Sagamihara-shi 252-0303, Kanagawa, Japan |
|                          | Tokyo Women’s Medical University Institutional Review Board, 8-1 Kawada-ko, Shinjuku-ku 162-8666, Tokyo, Japan |
|                          | Medical Corporation Kyowakai, Hannan Hospital Institutional Review Board, 277, Hando Minamino-cho, Naka-ku, Sakai 599-8263, Osaka, Japan |
|                          | Medical Corporation Houmankai Umezu Clinic Institutional Review Board, 2-6-12 Harada, Chikushino 818-0024, Fukuoka, Japan |
|                          | Takeda General Hospital Institutional Review Board 3-27 Yamagamachi, Aizu Wakamatsu 965-8585, Fukushima, Japan |
|                          | Fukuoka University Hospital Institutional Review Board 7-45-1 Nanakuma, Jyonan-ku, Fukuoka-shi 814-0180, Fukuoka, Japan |
| Central IRB - Poland     | Komisja Bioetyczna przy Bydgoskiej Izbie Lekarskiej ul. Powstadow Warszawy 11 85-681 Bydgoszcz |
| Central IRB - Romania    | Comisia Nationala de Etica pentru Studiul Clinic al Medicamentului, Str. Av. Sanatescu nr.48 Sector I Bucuresti |

(Continued)
| Local or central IRB/IEC | IRB/IEC Name |
|--------------------------|--------------|
| **Placebo-controlled, double-blind, randomized-withdrawal study** |
| Local IRB - South Korea | Institutional Review Board of The Catholic University of Korea 10, 63-ro, Yeongdeungpo-gu, 150-713, Republic of Korea  
Institutional Review Board of Eulji General Hospital, 68, Hangeulbiseok-ro, Nowon-gu, Seoul, 139-711 Republic of Korea  
Institutional Review Board of Jeju National University Hospital Aran 13gil 15, Jeju-si, Jeju Special Self-Governing Province, 690-767, Republic of Korea  
Chungnam National University Hospital, 282, Munhwa-ro, Jung-gu, Daejeon, 301-721, Republic of Korea  
Institutional Review Board of Korea University Anam Hospital 73 Inchon-ro, Seongbuk-Gu, Seoul, 136-705, Republic of Korea  
Institutional Review Board of Dongduk University Ilsan Hospital, 27 Dongduk-rom, Ilsandong-gu, Goyang-si, 410-773, Republic of Korea, Site 255  
Institutional Review Board of Hallym University Sacred Heart Hospital, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do, 431-070, Republic of Korea |
| Local IRB - Taiwan | Taipei City Hospital Institutional Review Board, No. 145, Zhengzhou Road, Taipei City, 103 Taiwan  
Chang Gung Medical Foundation Institutional Review Board No. 199, Tunhua North Road, Taipei City, 105 Taiwan |
| Central IRB - United States | Schulman Associates Institutional Review Board, 4445 Lake Forest Drive, Suite 300, Cincinnati, Ohio 45242 |
| Local IRB - United States | UC Irvine: Office of Research Institutional Review Board S171 California, Suite 150, Irvine, California 92697  
United States University at Buffalo: Health Ron Moscati Site 024 Sciences Institutional Review Board, 875 Ellicott Street, Buffalo, New York 14203  
Western Institutional Review Board, 3535 7th Avenue SW, Olympia, Washington 98502 |

| Open-label study |
|--------------------|-----------------------------|
| Central IRB USA | Schulman Associates Institutional Review Board, 4445 Lake Forest Drive Suite 300, Cincinnati, Ohio 45242 USA |
| Central IRB Canada Sites | Schulman Associates Institutional Review Board, 4445 Lake Forest Drive Suite 300, Cincinnati, Ohio 45242 USA |
| Central IRB France | Comité de Protection des Personnes Ile de France XI, Pavillon Jacques Courtois - 2ème étage, 20, rue Armagnis 78105 Saint Germain en Laye Cedex |
| Central IRB Hungary | Medical Research Council Ethics Committee of Clinical Pharmacology, (Égészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága), 1051 Budapest Arany János str. 6-8. |
| Local IRB Japan | Yuge Hospital Institutional Review Board 679-2 Yuge, Tatsuda-machi, Kita-ku, Kumamoto-city, Kumamoto, 861-8002, Japan  
Goryokai Medical Corporation Institutional Review Board, 6-2-3 9-jo, Shinora, Kita-ku, Sapporo-shi, 002-8029, Hokkaido, Japan |
| Local or central IRB/IEC | IRB/IEC Name |
|--------------------------|--------------|
| Placebo-controlled, double-blind, randomized-withdrawal study | |
| Seiwakai Medical Corporation Association Yutaka Clinic Institutional Review Board | 3-14-20 Sagamiono, Minami-ku, Sagamihara-shi 252-0303, Kanagawa, Japan |
| Unokai Medical Corporation Arakaki Hospital Institutional Review Board | 4-10-3 Ageda, Okinawa-city, 904-0012, Okinawa, Japan |
| Medical Corporation Houmankai Umezu Clinical Institutional Review Board | 2-6-12 Harada, Chikushino-shi, 818-0024, Fukuoka, Japan |
| Fukuoka University Hospital Institutional Review Board | 7-45-1 Nanakuma, Jyonan-ku, Fukuoka-shi, 814-0810, Fukuoka, Japan |
| Nagano Red Cross Hospital Institutional Review Board | 5-22-1, Wakasato, Nagano-shi, 380-8582, Nagano-ken, Japan |
| Shin Nihonbashi Ishii Clinic Institutional Review Board | 3rd Floor, Shin-Edobashi Building 8-6, Kobuna-cho, Nihonbashi, Chu-o-ku, 103-0024, Tokyo, Japan |
| National Hospital Organization Mito Medical Center Institutional Review Board | 280 Sakuranosato, Ibarakimachi, Higashiibaraki-gun, 311-3193, Ibaraki, Japan |
| Clinical Corporation Ikuseikai Shinozuka Institutional Review Board | 105-1 Shinozuka, Fujoka-shi, 375-0017, Gunma, Japan |
| Aino Clinic Institutional Review Board Osakaekimae saisian Building 18F | 1-1-3-1800, Umeda, Kita-ku, Osaka-shi, 530-0001, Osaka, Japan |
| Shida Hospital Institutional Review Board | 1-16-32 Annaka, Annaka-shi, 379-0116, Gunma, Japan |
| Asai Dermatology Clinic Institutional Review Board | 1-14 Katabiracho, Hodogaya-ku, Yokohama, 240-0013, Kanagawa, Japan |
| Seiwakai Medical Corporation Association Yutaka Clinic Institutional Review Board | 3rd Floor, 3-14-20, Sagamiono, Minami-ku, Sagamihara, 252-0303, Kanagawa, Japan |
| Sugihara Clinic Medical Corporation Institutional Review Board | 4-4-16-301 Honmachi, Kawaguchi-shi, 332-0012, Saitama, Japan |
| Nanko Kokoro no Clinic Institutional Review Board | 33 Sekibehikimebashi, Shirakawa, 962-0021, Fukushima, Japan |
| Shin-Abuyama Hospital Institutional Review Board | 4-10-1 Nasahara, Takatsuki, Osaka-shi, 569-1041, Osaka, Japan |
| Okayama Psychiatric Medical Center Institutional Review Board | 3-16 Shikatahonmachi, Kita-ku, Okayama-shi, 700-0915, Okayama, Japan |
| St. Mariana University Group Institutional Review Board | 2-16-1 Sugao, Miyamae-ku, Kawasaki-shi, 216-8511, Kanagawa, Japan |
| National Center of Neurology and Psychiatry (NCNP) Institutional Review Board | 4-1-1 Ogawahigashi-cho, Asahi-ku, Kodaira-shi, 187-8551, Tokyo, Japan |
| Nanbu Medical Center/Children Medical Center Institutional Review Board Arakawa | 118-1, Haebaruchuo, Shimajirigun, 901-1193, Okinawa, Japan |
| Kochi Medical School Hospital Institutional Review Board | 4-114 Showa-dori, Amagasaki-shi 660-0881, Hyogo, Japan |

(Continued)
| Local or central IRB/IEC | IRB/IEC Name |
|--------------------------|--------------|
| Placebo-controlled, double-blind, randomized-withdrawal study | Himorogi Psychiatric Institute, Medical Corporation Jisenkai Institutional Review Board, 2-31-3 Ichigaya Tamachi, Shinjuku-ku, 162-0843, Tokyo, Japan |
| Arakaki Hospital Institutional Review Board 4-10-3 Age da, Okinawa-shi, 904-0012, Okinawa, Japan |
| Medical Corporation YUSHINKAI Yushinkai Clinic Institutional Review Board, 2-12-12 Shinmori, Asahi-ku, Osaka-shi, 535-0022, Osaka, Japan |
| Okitama Public General Hospital Institutional Review Board, 2000 NishiOtsuka, Kawanishimachi, HigashiOkitamagun, 992-0601, Yamagata, Japan |
| Osaka City University Hospital Institutional Review Board, 1-5-7 Asahimachi, Abenoku, Osaka-city, 545-8586, Osaka, Japan |
| Nishi Hospital Institutional Review Board 3-2-18 Bingo-cho, Nada-ku, Kobe, 657-0037, Hyogo, Japan |
| Central IRB Malaysia | Medical Research & Ethics Committee (Health Ministry), Institut Pengurusan Kesihatan, Jalan Rumah Sakit, Bangsar, 59000 Kuala Lumpur Malaysia |
| Central IRB Poland | Bioethics Committee at the Regional Medical Chamber in Bydgoszcz (Komisja Bioetyczna przy Okregowej Izbie Lekarskiej w Bydgoszczy), ul. Powstańców Warszawy 11, 85-681 Bydgoszcz |
| Central IRB Romania | The National Bioethics Committee for Medicines and Medical Devices Soseaua Stefan cel Mare no. 19-21 SECTOR 2 BUCHAREST 020125 |
| Local IRB South Korea | Eulji General Hospital IRB, 68, Hangeulbiseok-ro, Nowon-gu, Seoul, 139-711, Republic of Korea |
| Jeju National University Hospital IRB Aran 13gil 15, Jeju-si, Jeju Special Self-Governing Province, 690-767, Republic of Korea |
| Korea University Anam Hospital IRB, 73, Inchon-ro, Seongbuk-gu, Seoul, 136-705, Republic of Korea |
| Dongguk University Ilsan Hospital IRB, 27, Dongguk-ro, Ilsandong-gu, Goyang-si, 410-773, Republic of Korea |
| Local IRB Taiwan | Taipei City Hospital Research Ethics Committee, Taipei, Taiwan |
| Local IRB United States | RGHS Clinical Investigation Committee 1425 Portland Ave, Rochester, NY 14621 |
| Northwestern University Institutional Review Board, Rubloff Building, 7th Floor, 750 N. Lake Shore Dr. Chicago, IL 6061 I |
| Dean Institutional Review Board, 2711 Allen Boulevard, Suite 300, Middleton, Wisconsin, 53562 |
| UB Institutional Review Board, 800 University Bay Drive, Suite 105 Madison, WI 53705 |
