

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 ≤ 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 ≤ 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.

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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.¹ Mood stabilizers and/or atypical antipsychotics are well accepted as the mainstays of bipolar-I disorder (BP-I) treatment.^{2–4} Compared with their oral counterparts, long-acting injectable (LAI) atypical antipsychotic formulations allow for better adherence with more consistent dosing^{2,4} and have recently shown to be more effective in preventing hospitalization of BP-I patients due to mental or physical illness.⁵ 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.⁶ Results from recent placebo-controlled⁷ and open-label⁸ 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.⁹ 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.¹⁰ The FAST has been shown to have strong psychometric properties and is able to detect differences between euthymic and acute patients with bipolar disorder.¹⁰ We have previously reported maintenance of improvement in FAST scores over 52 weeks in the AOM group of the placebo-controlled study.¹¹ Taking into account the FAST cut off scores proposed by Rosa et al,¹⁰ 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.⁷
2. An open-label, multicenter study (NCT01710709) conducted in 149 sites in 10 countries.⁸

Both studies^{7,8} 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.

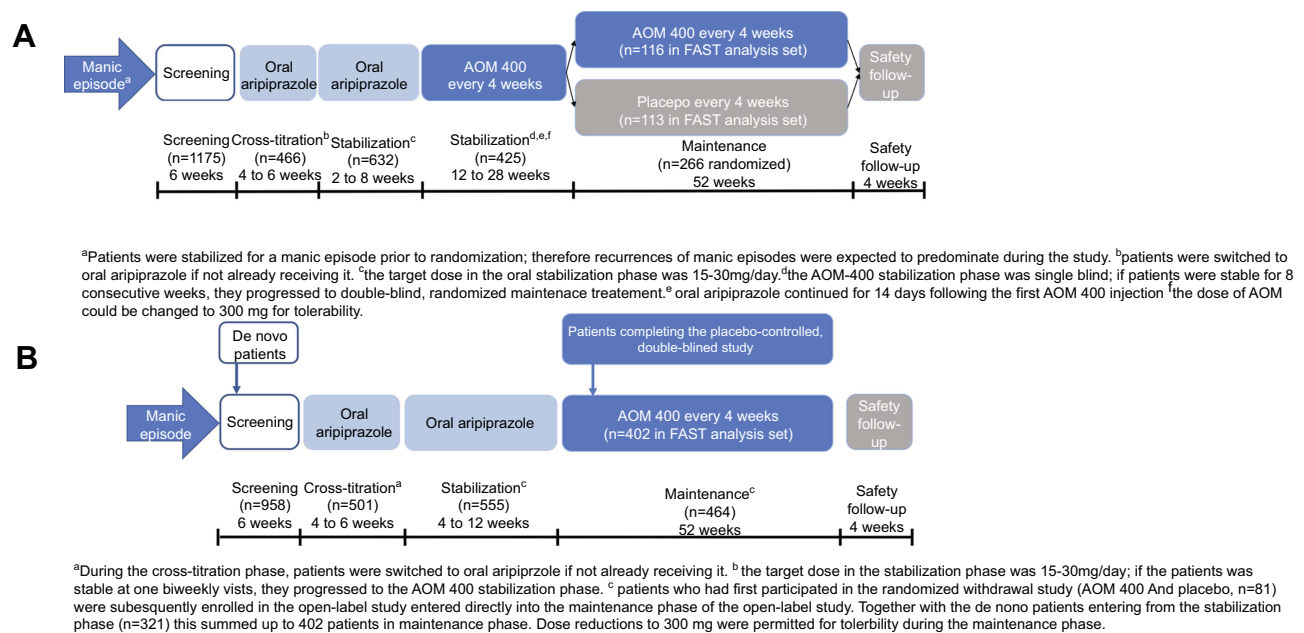


Figure 1 Study design. (A) Randomized-withdrawal study (Calabrese et al, 2017).⁷ (B) open-label maintenance study (Calabrese et al, 2018a).⁸

Abbreviation: AOM 400, Aripiprazole 400mg once-monthly.

Participants included in the open-label study were rolled over from the double-blind study or were AOM 400 treatment-naïve 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.¹⁰ 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.¹²

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 \pm 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).⁷ 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 .⁸

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 \pm 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 ,

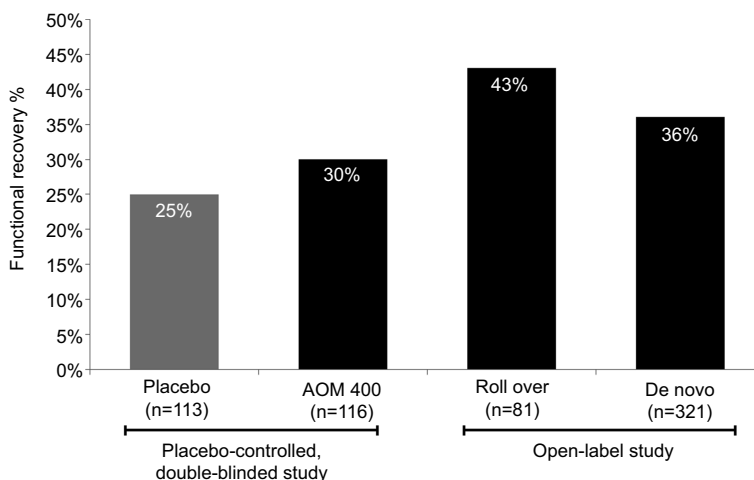


Figure 2 FAST recovery rates after long-term treatment with AOM 400 or placebo.

Abbreviations: FAST, Functioning Assessment Short Test; AOM 400, Aripiprazole 400 mg once monthly.

−0.44] at Week 52 was statistically significant ($p=0.028$). For those participants who met criteria for functional recovery, mean \pm SD 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 $4.09 \pm 4.00/3.59 \pm 3.39$ in the de novo group and $3.71 \pm 3.00/3.54 \pm 3.35$ 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,¹⁰ 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”.¹³ 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.¹¹

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.¹⁴ 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).¹⁵ 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.¹⁶ 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,⁹ 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	
	AOM 400	Placebo	Treatment effect (AOM vs placebo); LS mean [95% CI]	De novo	Rollover
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.¹² While LOCF analyses can be criticized, we used the same methods of imputation as per the primary study analyses.^{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.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.^{18–20} Almost all individuals with bipolar disorders require maintenance treatment to prevent subsequent episodes, reduce residual symptoms and restore functioning.⁴ The results of this study demonstrate the utility of a FAST total score of ≤ 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.^{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> 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 1. Taking responsibility for a household 2. Living on your own 3. Doing shopping 4. Taking care of yourself (physical aspects, hygiene)	FINANCIAL ISSUES 15. Managing your own money 16. Spending money in a balanced way
OCCUPATIONAL FUNCTIONING 5. Holding down a paid job 6. Accomplishing tasks as quickly as necessary 7. Working in the field in which you were educated 8. Occupational earnings 9. Managing the expected workload	INTERPERSONAL RELATIONSHIPS 17. Maintaining a friendship or friendships 18. Participating in social activities 19. Having good relationships with people close to you 20. Living together with your family 21. Having satisfactory sexual relationships 22. Being able to defend you interests
COGNITIVE FUNCTIONING 10. Ability to concentrate on a book, film 11. Ability to make mental calculations 12. Ability to solve a problem adequately 13. Ability to remember newly-learned names 14. Ability to learn new information	LEISURE TIME 23. Doing exercise or participating in sport 24. Having hobbies or personal interests

Note: Data from Rosa et al (2007).¹⁰

Table S2 List of institutional review boards (IRB) and/or independent ethics committees (IEC)

Local or central IRB/IEC	IRB/IEC Name
Placebo-controlled, double-blind, randomized-withdrawal study	
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, Sagami-hara-shi 252-0303, Kanagawa, Japan
	Tokyo Women's Medical University Institutional Review Board, 8-1 Kawada-cho, Shinjyuku-ku 162-8666, Tokyo, Japan
	Medical Corporation Kyowakai, Hannan Hospital Institutional Review Board, 277, Handa 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
	Japan Iwate Medical University Toru Sugiyama, 19-1m Uchimarui, Morioka-shi 020-8505, Iwate, Japan
	National Hospital Organization Hizen Psychiatric Center Institutional Review Board 160, Mitsu, Yoshinogari-cho, Kanzaki-gun 842-0192, Saga, Japan
	Nagasaki Medical Center of Psychiatry Institutional Review Board, 1575-2 Seibu Machi, Omura 856-0847, Nagasaki, Japan
Central IRB - Poland	Komisja Bioetyczna przy Bydgoskiej Izbie Lekarskiej ul. Powstancow Warszawy 1 85-681 Bydgoszcz
Central IRB - Romania	Comisia Nationala de Etica pentru Studiul Clinic al Medicamentului, Str. Av. Sanatescu nr:48 Sector 1 Bucuresti

(Continued)

Table S2 (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, 30"1-721, Republic of Korea
	Institutional Review Board of Korea University Anam Hospital 73 Incheon-ro, Seongbuk-Gu, Seoul, 136-705, Republic of Korea
	Institutional Review Board of Dongguk University Ilsan Hospital, 27 Dongguk-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
	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
	UC Irvine: Office of Research Institutional Review Board 5171 California, Suite 150, Irvine, California 92697
Local IRB - United States	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
	Louisiana State University Health Sciences Institutional Review Board, 433 Bolivar Street Suite 206, New Orleans, Louisiana 70112
Open-label study	
Central IRB USA	Schulman Associates Institutional Review Board, 4445 Lake Forest Drive Suite 300, Cincinnati, Ohio 45242 USA
	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 Armagis 78105 Saint Germain en Laye Cedex
Central IRB Hungary	Medical Research Council Ethics Committee of Clinical Pharmacology, (Egészségügyi 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, Shinoro, Kita-ku, Sapporo-shi, 002- 8029, Hokkaido, Japan

(Continued)

Table S2 (Continued).

Local or central IRB/ IEC	IRB/IEC Name
Placebo-controlled, double-blind, randomized-withdrawal study	
	Seiwakai Medical Corporation Association Yuraka Clinic Institutional Review Board 3-14-20 Sagamiono, Minami-ku, Sagami-hara-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 Umezaki Clinical Institutional Review Board, 2-6-12 Harada, Chikushino-shi, 818-0024, Fukuoka, Japan
	Fukuoka University Hospital Institutional Review Board, 7-45-1 Nanakuma, Jonan-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, Chuo-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, Fujioka-shi, 375-0017, Gunma, Japan
	Aino Clinic Institutional Review Board Osakaikimaedaisan Building 18F, 1-1-3-1800, Umeda, Kita-ku, Osaka-city, 530-0001, Osaka, Japan
	Shoda 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 Yuraka Clinic Institutional Review Board 3rd Floor, 3-14-20, Sagamiono, Minami-ku, Sagami-hara, 252-0303, Kanagawa, Japan
	Sugiyura 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-city, 569-1041, Osaka, Japan
	Okayama Psychiatric Medical Center Institutional Review Board, 3-16 Shikatahonmachi, Kita-ku, Okayama-shi, 700-0915, Okayama, Japan
	St. Marianna 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, Haebarucho, Shimajirigun, 901-1193, Okinawa, Japan
	Kochi Medical School Hospital Institutional Review Board, Kohasu Oko-cho, Nankoku, 783-8505, Kochi, Japan
	Kondo Hospital Institutional Review Board 4-114 Showa-dori, Amagasaki-shi 660-0881, Hyogo, Japan

(Continued)

Table S2 (Continued).

Local or central IRB/IEC	IRB/IEC Name
	Placebo-controlled, double-blind, randomized-withdrawal study
	Himorogi Psychiatric Institute, Medical Corporation Iseikai Institutional Review Board, 2-31-3 Ichigaya Tamachi, Shinjuku-ku, 162-0843, Tokyo, Japan
	Arakaki Hospital Institutional Review Board 4-10-3 Ageda, Okinawa-shi, 904-0012, Okinawa, Japan
	Medical Corporation YUSHINKAI Yushinkai Clinic Institutional Review Board, 2-12-12 Shimori, 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 Okręgowej Izbie Lekarskiej w Bydgoszczy), ul. Powstańców Warszaw 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, Incheon-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 60611
	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

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