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Early Placebo Improvement Is a Marker for Subsequent Placebo Response in Long-Acting Injectable Antipsychotic Trials for Schizophrenia:
Combined Analysis of 4 RCTs

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ABSTRACT

Objective: Placebo effects remain largely unexplored in clinical trials of long-acting injectable (LAI) antipsychotics for schizophrenia. This study aims to characterize patients showing improvements after placebo injections and to search for criteria for the prediction of subsequent response based on the magnitude of score changes after the first week of treatment.

Methods: Data from 450 patients with schizophrenia (*DSM-IV*) who received placebo injections in 4 double-blind randomized controlled trials evaluating efficacy of LAI paliperidone palmitate obtained through the Yale University Open Data Access (YODA) project were analyzed. These 4 studies were conducted from October 2003 to March 2008. Multiple logistic regression analyses were conducted to examine associations between placebo response and demographic and clinical characteristics. The predictive power of improvement at week 1 for response at week 9 was investigated; sensitivity and specificity of incremental 5% cutoff points between a 5% and 25% reduction in Positive and Negative Syndrome Scale (PANSS) total score at week 1 were calculated.

Results: Percent reduction in the PANSS total score at week 1 and a lower PANSS G12 item score (ie, better in judgment and insight) at baseline were significantly associated with placebo response at week 9 (odds ratio [OR] = 1.063; 95% CI, 1.040–1.087, $P < .001$; and OR= 0.739; 95% CI, 0.553–0.986, $P = .040$, respectively, in the per-protocol analysis). Cutoffs of a 10% (accuracy = 0.724 in the per-protocol analysis) and 15% (accuracy = 0.722 in the last-observation-carried-forward analysis) reduction in the PANSS total score at week 1 showed the highest predictive power.

Conclusions: The appreciation that longer-term response following placebo injections can be predicted by a 10%–15% PANSS total score reduction at week 1 could guide the design of future clinical trials of LAI antipsychotics in schizophrenia to identify and exclude potential placebo responders early during the course of the study.

J Clin Psychiatry 2019;80(1):18m12144

To cite: Kumagai F, Suzuki T, Fleischhacker WW, et al. Early placebo improvement is a marker for subsequent placebo response in long-acting injectable antipsychotic trials for schizophrenia: combined analysis of 4 RCTs. *J Clin Psychiatry.* 2019;80(1):18m12144.

To share: https://doi.org/10.4088/JCP.18m12144

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Response to placebo treatment in antipsychotic trials for schizophrenia has been increasing since 1960.[1] This increase obscures the true differences, if any, between drug and placebo treatments and has been identified as a potential explanation for an increasing number of failed clinical trials. In this respect, it is critically important to shed more light on placebo effects in this population and to improve our understanding of placebo response to optimize the design of clinical trials.

One of the obstacles to our understanding of placebo response is poor adherence, which is problematic even in well-controlled clinical trials. Indeed, according to a medication adherence analysis using a cohort of 16,907 participants from 95 clinical trials for various medical conditions, a significant proportion of the participants did not adhere to the study medications.[2] This lack of adherence may be particularly true for patients with schizophrenia, who frequently have difficulties in regularly taking pills due to their psychopathology, denial of the illness, and cognitive limitations. Consequently, insufficient adherence behavior is also relevant in placebo recipients in clinical trials involving schizophrenia patients. Long-acting injectable (LAI) antipsychotics provide a drug delivery option that allows for a reliable monitoring of adherence.[3] Depending on study design, they have been identified as at least as effective as or more efficacious than oral antipsychotics.[4,5] Therefore, placebo-controlled, double-blind trials of LAI antipsychotics provide an ideal dataset to shed further light on placebo effects, since adherence can easily be controlled for.

To maximize the information provided by clinical trials, it is critically important to identify and exclude potential placebo responders at the earliest opportunity. More recent studies have adopted a placebo lead-in period before randomization during which all participants are given placebo and those with a predefined placebo response are excluded from further procedures. However, the criteria for placebo response utilized have generally been arbitrary (eg, those showing a more than 20%

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Clinical Points

- Placebo effects remain largely unexplored in clinical trials of long-acting injectable (LAI) antipsychotics for schizophrenia.
- A 10%–15% improvement at week 1 was a reliable marker for subsequent placebo response (ie, ≥25% score reduction) at week 9. This cutoff may be a useful threshold for placebo lead-in phase to minimize trial failures for LAI antipsychotics.

reduction in Positive and Negative Syndrome Scale [PANSS] total score)[6] and not based on empirical data. Moreover, placebos used in the lead-in phases in clinical trials of LAIs are usually not injections, but oral pills, which is a concern in light of potential differences in placebo effects between oral tablets and injections.

Taking these issues taken into consideration, we conducted a post hoc analysis of 4 similarly designed placebo-controlled, double-blind, randomized controlled trials (RCTs) of LAI antipsychotics to identify potential placebo responders at the earliest opportunity and search for predictive criteria with regard to future placebo response. First, we attempted to characterize demographic and clinical attributes of placebo responders by using individual patient-level data. Second, we explored early prediction criteria for subsequent placebo response.

METHODS

Study Design

Datasets of 4 double-blind placebo-controlled RCTs evaluating the efficacy of long-acting injectable paliperidone palmitate were obtained through the Yale University Open Data Access (YODA) project (http://yoda.yale.edu).[7–10] The original studies are summarized in Table 1. All of them were funded by Johnson & Johnson Pharmaceutical Research & Development, LLC. Participants had a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), and had to score between 70 and 120 on the Positive and Negative Syndrome Scale (PANSS) at screening. Three studies included a screening period of up to 7 days (including up to 5 days to wash out disallowed psychotropic medications and/or 4 days for tolerability testing, if needed) and a 13-week double-blind treatment period.[7–9] The fourth study consisted of a screening period (up to 5 days, including 3-day washout of psychotropic medications other than antidepressants), followed by a 7-day open-label oral run-in period and a subsequent 64-day double-blind treatment period.[10] In 2 studies,[7,8] participants who showed a ≥25% decrease in PANSS total score during the screening period were excluded, and the other 2 studies[9,10] included only participants who had a PANSS total score of between 60 and 120 at baseline. In 1 study,[10] all of the participants also underwent a run-in period in which oral paliperidone was administered to confirm tolerability. After screening, all eligible participants were randomly assigned to either long-acting intramuscular injections of paliperidone palmitate or placebo injections. These original studies were approved at all participating sites, and written informed consent was obtained from the participants at study enrollment. Ethical approval was not sought for this specific post hoc analysis as we used completely anonymized data.

Statistical Analysis

Data used in the present analysis were derived from participants receiving placebo treatment. In this study, the PANSS was used as an outcome measure. Response was defined as a 25% or more reduction in the PANSS total score from baseline to week 9, which is the latest assessment time point available across the 4 studies. Participants who provided at least baseline and week 1 data were included because of our focus on the impact of score reduction from baseline to week 1 on the subsequent outcomes as described as follows.

First, a multiple logistic regression analysis was conducted to examine associations between placebo response and demographic and clinical characteristics that included sex, age (≤40 and >40 years), PANSS total scores at baseline, and percent score reduction in the PANSS total score from baseline to week 1. To further evaluate the impact of symptom domains on subsequent placebo response, additional multiple logistic regression analyses were run by replacing the PANSS

Table 1. Summary of Studies for the Present Analysis

Study	Study Duration	Main Inclusion Criteria	Sample Size
Kramer et al (2010)[10]	9 wk	Aged between 18 and 65 years; diagnosis of schizophrenia (*DSM-IV*); a PANSS total score of 70–120 at screening and 60–120 at baseline	N = 252 (active drug n = 163, placebo n = 84)
Gopal et al (2010)[8]	13 wk	Aged ≥18 years; diagnosis of schizophrenia (*DSM-IV*); a PANSS total score of 70–120 at screening and baseline; absence of a ≥25% decrease in PANSS total score between screening and baseline	N = 388 (active drug n = 252, placebo n = 136)
Nasrallah et al (2010)[7]	13 wk	Aged ≥18 years; diagnosis of schizophrenia (*DSM-IV*); a PANSS total score of 70–120 at screening and baseline; absence of a ≥25% decrease in PANSS total score between screening and baseline	N = 518 (active drug n = 391, placebo n = 127)
Pandina et al (2010)[9]	13 wk	Aged between 18 and 65 years; a diagnosis of schizophrenia (*DSM-IV*); a PANSS total score of 70–120 at screening and 60–120 at baseline	N = 652 (active drug n = 488, placebo n = 164)

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

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total score with the PANSS subscale scores, PANSS Marder 5-Factor scores,[11] and PANSS G12 (lack of judgment and insight) item score, respectively, in the above analysis.

Next, the prediction performance of binary classification of early improvement at week 1 (present or absent) for response at week 9 was examined. To this end, sensitivity, specificity, positive predictive value, and negative predictive value of the consecutive cutoff points in 5% increments between 5% and 25% in the PANSS total scores at week 1 were calculated. To seek the optimum cutoff point, accuracy, defined as (true positive + true negative)/total N, was calculated. Accuracy depends on the number of observations, which may render it inferior to careful and balanced consideration of sensitivity and specificity. To address this potential pitfall, cutoff points that demonstrated a level of at least 0.5 in both sensitivity and specificity with the highest degree of accuracy were examined.[12] In addition, the area under the curve of the receiver operating characteristic was also calculated.

To deal with missing values, both per-protocol (PP) analysis and last-observation-carried-forward (LOCF) analysis were considered. Statistical analyses were performed using R version 3.2.2. A P value of $<.05$ was considered to indicate statistical significance (2-tailed).

Table 2. Baseline Demographic and Clinical Characteristics of Participants (N = 450)

Characteristic	Value
Age group, n (%)	
≤ 20 y	9 (2.0)
21–30 y	83 (18.4)
31–40 y	127 (28.2)
41–50 y	144 (32.0)
> 50 y, ≤ 60 y	76 (16.9)
> 60 y	11 (2.4)
Male, n (%)	296 (65.8)
PANSS score, mean ± SD (range)	
Total	89.3 ± 11.9 (77–101)
Positive syndrome	21.9 ± 5.0 (17–27)
Negative syndrome	23.4 ± 4.7 (19–28)
General psychopathology	44.0 ± 6.9 (37–51)
PANSS Marder 5-Factor score, mean ± SD (range)	
Negative scale	22.2 ± 5.1 (17–27)
Positive scale	26.2 ± 5.2 (21–31)
Disorganized thought	20.7 ± 4.5 (16–25)
Uncontrolled hostility/excitement	9.2 ± 3.2 (6–12)
Anxiety/depression	10.9 ± 3.3 (8–14)

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

RESULTS

Sample Characteristics

A total of 509 participants were assigned to the placebo treatment groups in the 4 studies; of these, 452 participants were assessed at both baseline and week 1. Two participants lacked some PANSS item scores at baseline or week 1 and were therefore excluded. Thus, 450 participants were included for the purpose of this study. Their demographic and clinical characteristics are summarized in Table 2. A total of 210 participants remained in the trials until week 9; they were used for PP analysis. Proportions of placebo responders at week 9 were 46.7% (98/210) and 27.3% (123/450) in PP and LOCF analyses, respectively.

Factors Associated With Placebo Response at Week 9

Percent reduction in the PANSS total score from baseline to week 1 was significantly associated with subsequent response to placebo treatment at week 9 in both PP and LOCF analyses (Table 3). Moreover, this finding was replicated in additional multiple logistic regression analyses in which baseline PANSS total score was replaced with PANSS subscale scores, PANSS Marder 5-Factor scores, and PANSS G12 item score (Supplementary Tables 1–3). According to these additional analyses, lower PANSS G12 score (ie, better in judgment and insight) was significantly related to subsequent placebo response in both PP and LOCF analyses (OR = 0.739; 95% CI, 0.553–0.986; $P = .04$ in PP analysis and OR = 0.717; 95% CI, = 0.583–0.882; $P = .002$ in the LOCF analysis) (Supplementary Table 3). Moreover, greater PANSS Marder negative scale factor score was significantly associated with subsequent placebo response only in the LOCF analysis (OR = 1.064; 95% CI, = 1.008–1.123; $P = .023$), but not in the PP analysis (Supplementary Table 2). Any other baseline demographic or clinical features failed to show any significant associations with subsequent response at week 9.

Prediction of Placebo Response at Week 9 With Presence or Absence of Improvement at Week 1

The prediction performance of binary classification of early improvement at week 1 for response at week 9 is shown in Table 4. The 10% and 15% cutoffs in the PP and LOCF analyses, respectively, showed the highest degree of accuracy

Table 3. Association Between Demographic and Clinical Characteristics and Placebo Response at Week 9[a]

	Per-Protocol Analysis			LOCF Analysis		
Variable	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Age group						
≤ 40 y	1 (reference)			1 (reference)		
> 40 y	0.841	0.456–1.552	.580	0.985	0.625–1.552	.948
Sex						
Male	1 (reference)			1 (reference)		
Female	1.203	0.640–2.261	.566	1.086	0.674–1.751	.734
PANSS total score at baseline	0.999	0.972–1.027	.933	0.999	0.981–1.018	.146
PANSS total score % reduction at week 1	**1.063**	**1.040–1.087**	**<.001**	**138.5**	**35.0–548.8**	**<.001**

[a]Placebo response was defined as a 25% or more reduction in the total PANSS score from baseline to week 9. Statistically significant comparisons are shown in boldface.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

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Table 4. Predictive Performance of Score Reduction at Week 1 for Placebo Response at Week 9[a]

Analysis Method	Percentage Score Reduction at Week 1	PPV	NPV	Sensitivity	Specificity	Accuracy	AUC
Per-Protocol							0.77
	5%	0.62	0.81	0.85	0.55	0.690	
	10%	**0.69**	**0.75**	**0.73**	**0.71**	**0.724**	
	15%	0.73	0.71	0.62	0.79	0.714	
	20%	0.70	0.63	0.43	0.84	0.648	
	25%	0.79	0.62	0.35	0.92	0.652	
LOCF							0.76
	5%	0.39	0.91	0.86	0.50	0.600	
	10%	0.47	0.88	0.76	0.67	0.696	
	15%	**0.49**	**0.84**	**0.61**	**0.76**	**0.722**	
	20%	0.48	0.80	0.46	0.82	0.718	
	25%	0.55	0.79	0.37	0.88	0.744	

[a]Placebo response was defined as a 25% or more reduction in the PANSS total scores from baseline to week 9. Statistically significant values are shown in boldface.
Abbreviations: AUC = area under the curve, LOCF = last observation carried forward, NPV = negative predictive value, PANSS = Positive and Negative Syndrome Scale, PPV = positive predictive value.

for the prediction of response at week 9, still securing a level of at least 0.5 in terms of both sensitivity and specificity.

DISCUSSION

Summary of Results

The present analysis indicated that an improvement with placebo as early as week 1 serves to predict subsequent placebo response at week 9. Specifically, a 10%–15% reduction in the PANSS total score at week 1 was found to be a promising predictor of eventual placebo response later at week 9. Moreover, better insight into illness was significantly associated with greater placebo response, a novel finding to the best of our knowledge. These findings were confirmed in both PP and LOCF analyses. Our focus on response to an injectable form of placebo in schizophrenia trials represents a novel and significant strength of this work.

Early Symptom Improvement and Subsequent Response

Relations between early symptom improvements and subsequent response have been consistently reported in patients receiving active psychotropic drugs. Among patients with schizophrenia, early improvements, assessed with the PANSS or Brief Psychiatric Rating Scale (BPRS) total score, with antipsychotic treatment at week 2 predict response thereafter, whereas lack of early improvement at week 2 is associated with poor subsequent response to antipsychotics.[13–15] Similar findings have been found in patients with depression treated with antidepressants[16–18] and those with behavioral and psychological symptoms of dementia (BPSD) receiving antipsychotics.[19] On the other hand, there has been no previous study, to our knowledge, that investigated the impact of early improvement with placebo LAI treatment on subsequent placebo response in patients with schizophrenia. Our group recently conducted a similar analysis focusing on BPSD among patients with Alzheimer's disease and revealed that BPRS total score reductions by 10% at week 2 would be the best cutoff points to predict subsequent placebo response at week 8 with the highest degree of accuracy.[20] This finding from patients with BPSD seems compatible with our results, suggesting this phenomenon may be universal irrespective of psychiatric diagnoses or conditions. Recent clinical trials generally include a placebo lead-in period before randomization, in which all patients are given placebo medications and excluded if they show significant placebo response. However, the criteria for identification of placebo responders have been arbitrary. Our findings, which suggest that the cutoff point of 10% or 15% in the PANSS total score reduction at week 1 seems to be an accurate predictor of placebo response at week 9, could serve as a promising benchmark for such trial designs. Further clinical trials of LAI drugs are necessary to evaluate the usefulness of this cutoff value to more effectively exclude potential placebo responders in an effort to extract placebo-drug differences, if any such differences exist.

Baseline Characteristics Such as Insight and Placebo Response

We found that a lower PANSS G12 score (ie, better in judgment and insight) was significantly associated with placebo response in patients with schizophrenia receiving placebo injections. To the best of our knowledge, there has been no study that demonstrated this positive association. One potential reason for this finding is expectation bias on the side of the participants; patients with better insight are assumed to be more actively engaged in clinical trial procedures, and they may expect more from any form of medications, which in turn may have led to the greater placebo response that we observed in the present study.

A significant association was also found between placebo response and PANSS Marder negative scale score. However, this result should be interpreted with caution since it was observed only in the LOCF and not in the PP analysis. Moreover, we performed additional regression analyses to examine which of the PANSS subscales contained in the PANSS Marder negative scale (ie, PANSS N1, N2, N3, N4, N6, G7, and G16) would be associated with subsequent placebo response, but failed to find any association of placebo response with any single items.

Limitations

The results of this study need to be interpreted in light of several limitations. First, the 4 studies included in this study were not originally designed to examine placebo response, and this study was a post hoc analysis. Second, the choice of not week 2 but week 1 for the current analysis was determined post hoc based on the available assessments in common across the 4 studies. In addition, the choice of a 25% improvement

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as response may be considered arbitrary. We therefore performed additional analyses to examine the relationship between the improvement at week 1 and response defined as a 50% improvement at week 9. The results showed that the PANSS total score percent reduction at week 1 was consistently associated with subsequent placebo response, while the PANSS G12 score at baseline did not show any association with placebo response at week 9 (Supplementary Tables 4–7). In addition, the cutoff of a 20% reduction in the PANSS total score at week 1 showed the highest predictive power in the LOCF and PP analyses (Supplementary Table 8). Third, a significant number of patients dropped out prematurely, which is a source of concern, although both PP and LOCF analyses provided comparable results. Fourth, the study duration of 9 weeks may be considered short with LAIs in the management of schizophrenia, and the results may pertain only to paliperidone palmitate. Fifth, we did not have data on personality characteristics and cognitive function of the subjects, which are thought to impact placebo effects. Moreover, data on medications that the subjects were receiving before entering the studies were not available. Subjects who received high doses of antipsychotics prior to the studies may have experienced improvements during an initial period on placebo. In addition, while the subjects were apparently symptomatic (Table 1), there was no relevant information as to whether illness was acutely exacerbated. This issue has to be seriously taken into consideration especially with regard to generalizability of the results in the present study. Finally, the choice of variables included in multiple logistic regression analyses was based on clinical relevance, but may be considered arbitrary. We included a limited number of variables in the analysis since inclusion of too many factors in one model would have resulted in low statistical power.

CONCLUSION

The present study indicated that an early improvement on placebo represented by a 10%–15% reduction in the PANSS total score at week 1 and better insight at baseline predicts subsequent placebo response at week 9. Further prospective clinical trials of LAI drugs are needed to replicate these findings, and the impact of other potentially relevant factors, including personality characteristics and cognitive function, on placebo response warrants future investigations. These caveats notwithstanding, the results of this study provide critical insights to aid with the design of future studies of antipsychotics in patients with schizophrenia.

Submitted: January 23, 2018; accepted July 16, 2018.

Published online: December 4, 2018.

Potential conflicts of interest: **Dr Suzuki** has received manuscript or speaker's fees from Dainippon Sumitomo, Eli Lilly, Elsevier Japan, Janssen, Meiji Seika, Otsuka, Wiley Japan, and Yoshitomi Yakuhin within the past 3 years.. **Dr Fleischhacker** has received grants from Otsuka, Pfizer, Janssen, and Reckitt-Benckiser; is a stock shareholder in Richter Gedeon; has received speaker's honoraria from Lundbeck, Roche, Recordati, Janssen, Otsuka, and Richter; and has received consulting honoraria from Acadia, Lundbeck, Roche, Otsuka, Janssen, Richter, Teva, Dainippon Sumitomo, and Takeda. **Dr Yasui-Furukori** has received speaker's fees from Mochida, Dainippon Sumitomo, and MSD within the past 3 years. **Dr Mimura** has received grants and/or speaker's honoraria from Asahi Kasei, Astellas, Daiichi Sankyo, Dainippon-Sumitomo, Eisai, Eli Lilly, Fuji Film RI, Janssen, Kracie, Meiji-Seika, Mochida, MSD, Novartis, Ono Yakuhin, Otsuka, Pfizer, Shionogi, Takeda Yakuhin, Tanabe Mitsubishi, and Yoshitomi Yakuhin within the past 3 years. **Dr Uchida** has received grants from Eisai, Otsuka, Dainippon-Sumitomo, Mochida, Meiji-Seika, and Novartis; speaker's honoraria from Otsuka, Eli Lilly, Shionogi, Pfizer, Yoshitomi Yakuhin, Daiippon-Sumitomo, Meiji-Seika, MSD, and Janssen; and advisory panel payments from Dainippon-Sumitomo Pharma within the past 3 years. **Dr. Kumagai** has no conflicts of interest.

Funding/support: None.

Disclaimer: This study, carried out under Yale University Open Data Access (YODA) Project #2017-1701, used data obtained from the YODA Project, which has an agreement with Janssen Research & Development, LLC. The data are owned by Johnson & Johnson Pharmaceutical Research & Development LLC. The access to the data was requested through YODA project (http://yoda.yale.edu/). The interpretation and reporting of research using these data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or Janssen Research & Development, LLC.

Acknowledgments: The authors appreciate Larry Alphs, MD, PhD (Janssen Scientific Affairs, LLC, Titusville, New Jersey), for his guidance regarding YODA project and Ms Aki Endo (Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan) and Ms Ai Gounaridis (Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan) for their administrative support. All of them have nothing to disclose regarding conflict of interest.

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Early Placebo Improvement Is a Marker for Subsequent Placebo Response in Long-Acting Injection Trials for Schizophrenia: Combined Analysis of Four RCTs

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DOI Number: https://doi.org/10.4088/JCP.18m12144

List of Supplementary Material for the article

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Supplementary Table 1. Association Between Clinical Variables with a Focus on PANSS subscale score and Placebo Response[a] at Week 9

	PP analysis			LOCF analysis		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age group						
≦40	1 (reference)			1 (reference)		
> 40	0.833	0.450-1.545	0.563	1.000	0.633-1.580	0.999
Gender						
Male	1 (reference)			1 (reference)		
Female	1.219	0.645-2.306	0.542	1.064	0.658-1.719	0.801
PANSS total score %reduction at week		**1.042-1.090**	**<0.001**			
1	**1.066**			**157.0**	**38.7-636.9**	**<0.001**
PANSS subscale score at baseline						
Positive scale	1.006	0.931-1.087	0.874	0.970	0.920-1.022	0.253
Negative scale	1.060	0.981-1.145	0.141	1.018	0.963-1.075	0.533
General Psychopathology scale	0.972	0.918-1.030	0.336	1.007	0.967-1.048	0.750

[a] Response was defined as a 25% or more reduction in the total PANSS score from baseline to week 9

[b] p-value of <0.05 was shown in bold.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PP, per protocol; LOCF last-observation-carried-forward

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Supplementary Table 2. Association Between Clinical Variables with a Focus on PANSS Marder 5-factor and Placebo Response[a] at Week 9

	PP analysis			LOCF analysis		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age group						
≦40	1 (reference)			1 (reference)		
> 40	0.845	0.454-1.575	0.597	0.983	0.616-1.567	0.942
Gender						
Male	1 (reference)			1 (reference)		
Female	1.255	0.654-2.406	0.495	1.084	0.662-1.773	0.749
PANSS total score %reduction at week 1	**1.065**	**1.041-1.090**	**<0.001**	**133.3**	**32.3-551.7**	**<0.001**
PANSS Marder 5-Factor at baseline						
Negative scale	0.167	0.986-1.156	0.109	**1.064**	**1.008-1.123**	**0.023**
Positive scale	0.966	0.898-1.040	0.358	0.951	0.903-1.001	0.056
Disorganized thought	0.956	0.872-1.048	0.339	0.956	0.903-1.018	0.260
Uncontrolled hostility/excitement	1.084	0.968-1.214	0.163	1.038	0.960-1.123	0.353
Anxiety/depression	0.971	0.875-1.078	0.582	1.044	0.969-1.125	0.261

[a] Response was defined as a 25% or more reduction in the total PANSS score from baseline to week 9

[b] p-value of <0.05 was shown in bold.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PP, per protocol; LOCF last-observation-carried-forward

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Supplementary Table 3. Association Between Clinical Variables with a Focus on PANSS G12 score and Placebo Response[a] at Week 9

	PP analysis			LOCF analysis		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age group						
≦40	1 (reference)			1 (reference)		
> 40	0.741	0.396-1.385	0.348	0.865	0.543-1.379	0.542
Gender						
Male	1 (reference)			1 (reference)		
Female	1.293	0.682-2.451	0.432	1.173	0.723-1.903	0.519
PANSS total score %reduction at week 1	**1.065**	**1.041-1.089**	**<0.001**	**144.327**	**35.6-584.8**	**<0.001**
PANSS G-12 score at baseline	**0.739**	**0.553-0.986**	**0.040**	**0.717**	**0.583-0.882**	**0.002**

[a] Response was defined as a 25% or more reduction in the total PANSS score from baseline to week 9

[b] p-value of <0.05 was shown in bold.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PP, per protocol; LOCF last-observation-carried-forward

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Supplementary Table 4. Association Between Demographic and Clinical Characteristics and ≥50% improvement[a] at Week 9

	PP analysis			LOCF analysis		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age group						
≦40	1 (reference)			1 (reference)		
> 40	0.584	0.252-1.353	0.210	0.575	0.273-1.212	0.146
Gender						
Male	1 (reference)			1 (reference)		
Female	1.474	0.612-3.554	0.387	1.238	0.560-2.739	0.598
Total PANSS score at baseline	0.968	0.931-1.006	0.102	0.977	0.947-1.008	0.146
PANSS total score %reduction at week 1	**1.056**	**1.032-1.082**	**<0.001**	**154.4**	**23.0-1038.4**	**<0.001**

[a] in the total PANSS score from baseline to week 9

[b] p-value of <0.05 was shown in bold.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PP, per protocol; LOCF last-observation-carried-forward

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Supplementary Table 5. Association Between Clinical Variables with a Focus on PANSS subscale score and ≥50% improvement[a] at Week 9

	PP analysis			LOCF analysis		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age group						
≦40	1 (reference)			1 (reference)		
> 40	0.588	0.251-1.378	0.222	575	0.272-1.214	0.147
Gender						
Male	1 (reference)			1 (reference)		
Female	1.541	0.632-3.759	0.342	1.208	0.544-2.680	0.643
PANSS total score %reduction at week 1	**1.061**	**1.035-1.090**	**<0.001**	**189.4**	**26.4-1361.2**	**<0.001**
PANSS subscale score at baseline						
Positive scale	0.988	0.887-1.100	0.822	0.960	0.880-1.046	0.350
Negative scale	1.056	0.948-1.176	0.319	1.010	0.922-1.107	0.827
General Psychopathology scale	0.928	0.858-1.003	0.061	0.973	0.911-1.040	0.421

[a] in the total PANSS score from baseline to week 9

[b] p-value of <0.05 was shown in bold.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PP, per protocol; LOCF last-observation-carried-forward

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Supplementary Table 6. Association Between Clinical Variables with a Focus on PANSS Marder 5-factor and ≥50% improvement[a] at Week 9

	PP analysis			LOCF analysis		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age group						
≦40	1 (reference)			1 (reference)		
> 40	0.567	0.238-1.347	0.198	0.552	0.257-1.186	0.128
Gender						
Male	1 (reference)			1 (reference)		
Female	1.588	0.637-3.956	0.321	1.251	0.556-2.813	0.588
PANSS total score %reduction at week 1	**1.060**	**1.033-1.087**	**<0.001**	**188.8**	**25.3-1411.1**	**<0.001**
PANSS Marder 5-Factor at baseline						
Negative scale	1.080	0.966-1.208	0.174	1.047	0.960-1.142	0.299
Positive scale	0.978	0.888-1.078	0.659	0.978	0.902-1.060	0.586
Disorganized thought	0.910	0.808-1.025	0.122	0.938	0.848-1.037	0.212
Uncontrolled hostility/excitement	0.944	0.813-1.095	0.452	0.947	0.835-1.074	0.397
Anxiety/depression	0.909	0.789-1.046	0.183	0.954	0.847-1.075	0.442

[a] in the total PANSS score from baseline to week 9

[b] p-value of <0.05 was shown in bold.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PP, per protocol; LOCF last-observation-carried-forward

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Supplementary Table 7. Association Between Clinical Variables with a Focus on PANSS G12 score and ≥50% improvement[a] at Week 9

	PP analysis			LOCF analysis		
Variables	Odds Ratio	95%CI	p-value[b]	Odds Ratio	95%CI	p-value[b]
Age group						
≦40	1 (reference)			1 (reference)		
> 40	1.530	0.663-3.530	0.319	0.602	0.285-1.273	0.184
Gender						
Male	1 (reference)			1 (reference)		
Female	0.761	0.321-1.806	0.535	1.187	0.538-2.618	0.672
PANSS total score %reduction at week 1	**1.054**	**1.030-1.079**	**<0.001**	**161.6**	**24.3-1075.7**	**<0.001**
PANSS G-12 score at baseline	0.971	0.654-1.440	0.884	0.994	0.711-1.390	0.972

[a] in the total PANSS score from baseline to week 9

[b] p-value of <0.05 was shown in bold.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PP, per protocol; LOCF last-observation-carried-forward

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Supplementary Table 8. Prediction Performance of Score Reduction at Week 1 for ≥50% improvement[a] at Week 9

Analysis method used	Percentage score reduction at week 1	PPV	NPV	Sensitivity	Specificity	Accuracy	AUC
PP analysis	5%	0.21	0.96	0.90	0.41	0.48	
	10%	0.24	0.94	0.81	0.56	0.60	
	15%	0.26	0.93	0.71	0.66	0.66	0.75
	20%	**0.30**	**0.92**	**0.61**	**0.76**	**0.73**	
	25%	0.31	0.90	0.45	0.83	0.77	
LOCF analysis	5%	0.12	0.98	0.91	0.42	0.46	
	10%	0.14	0.98	0.83	0.58	0.60	
	15%	0.16	0.97	0.71	0.69	0.70	0.77
	20%	**0.18**	**0.96**	**0.63**	**0.76**	**0.75**	
	25%	0.20	0.95	0.49	0.83	0.80	

[a] in the PANSS total scores from baseline to week 9

Abbreviations: AUC, area under the curve; LOCF, last-observation-carried-forward; NPV, negative predictive value; PANSS, Positive and Negative Syndrome Scale; PP, per protocol; PPV, positive predictive value

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