

Successful switching of patients with acute schizophrenia from another antipsychotic to brexpiprazole: comparison of clinicians' choice of cross-titration schedules in a post hoc analysis of a randomized, double-blind, maintenance treatment study

Christoph U. Correll ¹, * Lily Shi,² Catherine Weiss,² Mary Hobart,² Anna Eramo,³ Ruth A. Duffy,² Emmanuelle Weiller,⁴ and Ross A. Baker²

¹ Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, New York; and Recognition and Prevention (RAP) Program, Zucker Hillside Hospital, Northwell Health, Glen Oaks, New York; Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry, Berlin, Germany

² Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, New Jersey

³ Lundbeck LLC, Deerfield, Illinois

⁴ H. Lundbeck A/S, Valby, Copenhagen, Denmark (at the time of this work)

Objective. To compare the tolerability and efficacy of different antipsychotic cross-titration schedules, using data from a brexpiprazole study (Equator; NCT01668797).

Methods. Patients with schizophrenia were cross-titrated from other antipsychotics to brexpiprazole monotherapy in a 1–4 week open-label conversion phase, then entered a single-blind brexpiprazole treatment phase. Patients were stratified into four “conversion groups,” according to the amount of time spent in the conversion phase. Discontinuation rates, treatment-emergent adverse events (TEAEs), and efficacy (Positive and Negative Syndrome Scale [PANSS]) were compared between conversion groups.

Results. Of the 404 patients treated with brexpiprazole, the majority (72.0%) spent 22–33 days in the conversion phase. Discontinuation rates due to lack of efficacy or adverse events were low in all conversion groups. Of the 292 patients who successfully switched and completed 8 weeks of brexpiprazole treatment, most were converted to brexpiprazole over 22–33 days (80.1%), and fewer were converted over 1–7 days (2.4%), 8–14 days (6.5%), or 15–21 days (11.0%). The incidence of TEAEs over 8 weeks was lower among those converted over 22–33 days (44.4%) than in other conversion groups (62.5–84.2%), although low patient numbers with shorter conversion times limit the generalizability of this finding. Each conversion group showed comparable improvement in PANSS total score from baseline.

Conclusion. The majority of patients were cross-titrated to brexpiprazole over a period of 22–33 days, by investigators' choice. Additional data on shorter conversions may help clinicians to choose a switching paradigm that best meets their patients' needs.

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* Address for correspondence: Christoph U. Correll, Zucker Hillside Hospital, Psychiatry Research, 75–59 263rd Street, Glen Oaks, New York 11004.

(E-mail: ccorrell@northwell.edu)

Introduction

Schizophrenia is a severe and chronic disease, with varying presentation, course, and response to treatment

among patients. Switching antipsychotic medications is common in the management of schizophrenia, for reasons including unsatisfactory response, relapse (despite compliance), or intolerability due to adverse events.^{1–4} Many different switching strategies can be conceived, according to the speed of titration and the degree of overlap between agents.⁵ Switching strategies are of varying complexity and have differing risks of drug interactions, subtherapeutic dosing, and withdrawal or rebound symptoms.^{1,2,5,6} Cross-titration, involving the gradual dose escalation of a new antipsychotic with overlapping gradual discontinuation of the previous antipsychotic,⁵ is the preferred switching method for oral atypical antipsychotics according to a panel of experts in the treatment of schizophrenia.⁷ In particular, “plateau” cross-titration, involving the gradual dose escalation of new antipsychotic with *delayed* gradual discontinuation of the previous antipsychotic (only after a therapeutic dose of the new antipsychotic has been reached and 4–5 half-lives of the previous antipsychotic have passed), has been proposed as the best strategy to avoid rebound phenomena,^{5,8} although this is not supported by current evidence from randomized controlled trials that may not reflect patients and treatment strategies in clinical care.⁹ For example, plateau cross-titration may minimize the rebound psychosis, mania, or agitation that can occur when switching from a full dopamine D₂ antagonist to a partial D₂ agonist, and the rebound anxiety, insomnia, agitation, and restlessness that can occur when switching from an antipsychotic with more potent antihistaminergic or anticholinergic activity to one with less antihistaminergic or anticholinergic activity.^{6,8} Taking into account these recommendations, individualized switching strategies should be devised based on the properties of the antipsychotics involved (e.g., efficacy, tolerability, dosing schedule, pharmacodynamics, and pharmacokinetics), as well as patient factors (e.g., past response and severity of illness).^{2,8}

Brexpiprazole is a serotonin–dopamine activity modulator that acts as a partial agonist at serotonin 5-HT_{1A} and dopamine D₂ receptors and as an antagonist at serotonin 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, all with subnanomolar potency.¹⁰ The efficacy and safety of brexpiprazole have been demonstrated in a phase 3 schizophrenia program comprising two acute studies^{11,12} and a maintenance study.¹³ Brexpiprazole is approved in the United States, Canada, Australia, and Japan for the treatment of schizophrenia, and in the United States as an adjunctive therapy to antidepressants for the treatment of major depressive disorder.

Due to the design of the acute studies for regulatory approval, in which patients were washed out from prior antipsychotics before brexpiprazole was initiated, these studies generated no data on switching strategies or outcomes.^{11,12} In contrast, the brexpiprazole

maintenance study included a 1–4 week conversion phase in which patients on previous antipsychotic(s) were cross-titrated to brexpiprazole monotherapy.¹³ The aim of the present analysis was to use data from the maintenance study to compare the tolerability and efficacy of different clinicians’ choice of cross-titration schedules to aid clinicians in choosing a switching schedule to brexpiprazole monotherapy that best meets their patients’ needs.

Methods

Study design and patients

This was a post hoc analysis of data from a multicenter, randomized, double-blind, placebo-controlled phase 3 maintenance withdrawal study (Equator; NCT01668797).¹³ For a full description of the study design and selection criteria, please refer to Fleischhacker and colleagues’ 2017 publication.¹³ The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline and local regulatory requirements. The protocol was approved by an institutional review board or independent ethics committee for each investigational site, and all patients provided written informed consent to participate.

The study included male and female patients aged 18–65 years with a diagnosis of schizophrenia for at least 3 years as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR)¹⁴ and confirmed by the Mini International Neuropsychiatric Interview (MINI) for Schizophrenia and Psychotic Disorders Studies.¹⁵ Patients had to have been experiencing an acute exacerbation of psychotic symptoms at screening, as demonstrated by a Positive and Negative Syndrome Scale (PANSS)¹⁶ total score of >80. Patients had to have shown a response to antipsychotic treatment (other than clozapine) in the previous year, had to be currently being treated with oral or depot antipsychotics (other than clozapine) or to have a recent lapse in antipsychotic treatment, and had to have a history of relapse and/or symptom exacerbation in the absence of antipsychotic treatment. Exclusion criteria included a DSM-IV-TR Axis I diagnosis other than schizophrenia, acute depressive symptoms in the previous 30 days requiring antidepressant therapy, antipsychotic-resistant or refractory schizophrenia, a significant risk of violent behavior or suicide, meeting DSM-IV-TR criteria for substance abuse or dependence in the previous 180 days, or requiring prohibited concomitant therapy during the trial.

The study comprised a screening phase, an open-label phase for conversion from other antipsychotics to monotherapy with oral brexpiprazole (and washout of prohibited concomitant medications), a single-blind

treatment phase to stabilize patients on oral brexpiprazole, a double-blind maintenance treatment phase (in which patients were randomized to oral brexpiprazole or placebo), and a safety follow-up phase. Following screening, eligible patients entered the conversion phase if they were currently receiving antipsychotics or other prohibited concomitant medications (Table 1); otherwise, they entered the stabilization phase directly. During the conversion phase, patients were converted to once-daily brexpiprazole over 1–4 weeks, as outlined in Table 1. Simultaneously, previous antipsychotic treatment and any prohibited medications were discontinued. Patients completing the conversion phase, and patients not requiring conversion, entered a 12–36 week stabilization phase. In this phase, patients were titrated to a dose of brexpiprazole (1–4 mg/d) that would maintain stability of psychotic symptoms while minimizing tolerability issues.

This post hoc analysis focused on a time frame of 8 weeks after the first dose of brexpiprazole, covering the conversion phase and the start of the stabilization phase. A subsample comprising all patients in whom at least 8 weeks of brexpiprazole treatment was achieved was chosen to explore: (1) which of the clinicians' chosen switching strategies were the most represented among the successful switches from prior antipsychotic

treatment to brexpiprazole; and (2) whether any baseline patient or treatment differences existed among the different naturalistically employed, successful switching strategies.

Assessments

In this post hoc analysis, tolerability was assessed by the time to, and reasons for, discontinuation, and the incidence of treatment-emergent adverse events (TEAEs). Efficacy was assessed using the PANSS and the Clinical Global Impressions–Severity of illness (CGI-S) scale. The PANSS is a clinician-rated scale that measures positive, negative, and general psychopathology symptoms, scored from 30 to 210, where a higher score indicates greater psychopathology.¹⁶ The CGI-S is a clinician-rated scale that measures global illness severity, scored from 1 (not at all ill) to 7 (among the most extremely ill).¹⁷ The PANSS and CGI-S were administered at the baseline visit and last visit of the conversion phase and at every 2 weeks during the stabilization phase.

Statistical analyses

This post hoc analysis included patients who received at least 1 dose of brexpiprazole during the conversion

TABLE 1. Strategy of switching to brexpiprazole monotherapy during the conversion phase, according to antipsychotic or other prohibited concomitant medication at screening

Reason for entering conversion phase	Switching instructions
Patient was currently receiving oral aripiprazole (dosed within 14 days of screening). Patient was currently receiving another oral antipsychotic (other than clozapine) (dosed within 7 days of screening).	Initiate on brexpiprazole 1 mg/d. Over 1–4 weeks, according to the investigator's judgment, adjust brexpiprazole within the range of 1–4 mg/d while gradually reducing the dose of other antipsychotic.
Patient was currently receiving an LAI antipsychotic (dosed within 1.5 cycles ^a of screening).	Initiate on brexpiprazole 1 mg/d. Over 1–4 weeks, according to the investigator's judgment, adjust brexpiprazole within the range of 1–4 mg/d until a time period equal to 1.5 LAI cycles has elapsed.
Patient was currently receiving other prohibited concomitant medications: ◆ all psychotropic agents, including antidepressants, OFC, mood stabilizers, and benzodiazepines ^b ◆ ramelteon and other non-benzodiazepine sleep aids ^c ◆ antihistamines ^d ◆ varenicline ◆ vitamins, nutritional supplements, and nonprescription herbal preparations ^e ◆ CYP2D6 inhibitors and CYP3A4 inhibitors and inducers ◆ investigational agents.	Initiate on brexpiprazole 1 mg/d. Over 1–4 weeks, according to the investigator's judgment, adjust brexpiprazole within the range of 1–4 mg/d.

LAI = long-acting injectable; OFC = olanzapine–fluoxetine combination.

^a Cycle length was based on the prescribing label. If the required washout was >28 days, the patient was kept in the screening phase for up to 14 days until ≤28 days were remaining.

^b Except lorazepam or oxazepam (clonazepam or diazepam, if not available) used as a rescue medication.

^c Except zolpidem, zaleplon, zopiclone, and eszopiclone for the treatment of insomnia.

^d Except loratadine and cetirizine.

^e Unless approved in advance by the medical monitor.

phase. Patients were stratified into four “conversion groups” according to the amount of time spent in the conversion phase: 1–7 days, 8–14 days, 15–21 days, and 22–33 days (up to 33 days rather than 28 days to allow for minor variations in visit timings). Patients in each group were followed for up to 8 weeks from the start of the conversion phase (their first dose of brexpiprazole). Eight weeks of brexpiprazole treatment was chosen so that patients in each conversion group had the same exposure to brexpiprazole, and with sufficient time to assess efficacy. Depending on the amount of time spent in the conversion phase, 8 weeks of brexpiprazole treatment comprised 1–4 weeks in the conversion phase and 4–7 weeks in the stabilization phase (Figure 1).

The four conversion groups were compared in terms of time to discontinuation for different reasons within the first 8 weeks of brexpiprazole treatment, plotted as Kaplan–Meier survival analysis curves. This analysis was performed to identify any differences in discontinuation rates according to the speed of cross-titration from a prior antipsychotic to brexpiprazole.

Next, the conversion groups were further split, as follows: (1) patients who converted to brexpiprazole (i.e., completed the conversion phase) and also completed 8 weeks of brexpiprazole treatment, (2) patients who converted to brexpiprazole but discontinued in <8 weeks, and (3) patients who discontinued prior to converting to brexpiprazole (i.e., discontinued during the conversion phase). These various subgroups were generated in order to identify the differences between patients who successfully converted to brexpiprazole and those who did not, in terms of reason for discontinuation, baseline demographic and clinical characteristics, type of baseline concomitant antipsychotic, and the incidence of TEAEs. Thus, these analyses were performed to assess the generalizability

of the findings, to identify risk factors for early discontinuation, and to identify characteristics that may be less represented in the analyzed sample.

Finally, in the group of patients who converted to brexpiprazole and completed 8 weeks of brexpiprazole treatment, the change from baseline in PANSS total score and CGI-S score were calculated for each conversion group.

In general, descriptive statistics are presented; due to the differences in sample size between groups, further statistical analysis was considered inappropriate. A chi-squared test was used to assess differences in baseline concomitant antipsychotic use between groups. One-way analysis of variance (ANOVA) was used to compare changes from baseline in PANSS total and CGI-S scores between conversion groups.

Results

Patient disposition

A total of 404 patients received at least 1 dose of brexpiprazole during the conversion phase and were included in this analysis. All patients were currently receiving at least one antipsychotic other than brexpiprazole at baseline, and, therefore, no patients entered the conversion phase based on prohibited concomitant medications alone.

Of the 404 patients treated with brexpiprazole (Figure 1), the majority (72.0%) spent 22–33 days in the conversion phase. Only a small number of patients spent 1–7 days (4.2%), 8–14 days (10.4%), or 15–21 days (13.4%) in the conversion phase.

Times to discontinuation from the start of the conversion phase to 8 weeks are presented in Figure 2: (a) due to all reasons other than the sponsor terminated the study (in this maintenance study, efficacy [as

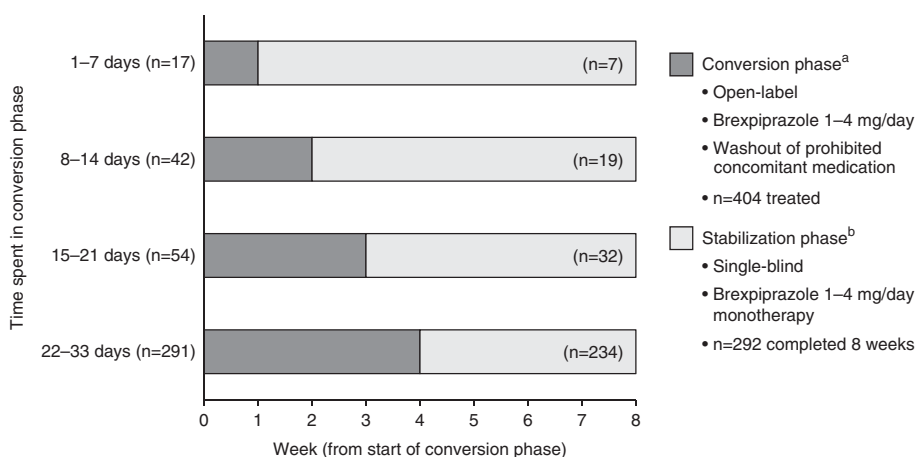
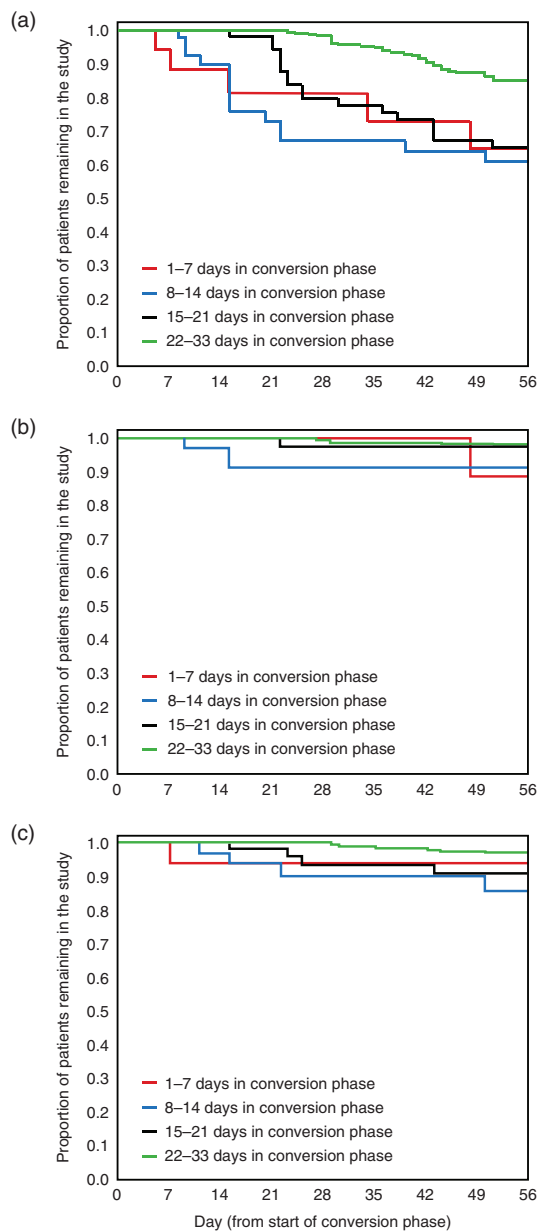


FIGURE 1. Definition of conversion groups, with patient flow through the conversion and stabilization phases. Data for patients who received at least 1 dose of brexpiprazole in the conversion phase. ^aWeekly visits; ^bweekly visits for 4 weeks, every two weeks thereafter.



Number of patients at risk									
1-7 days	17	16	12	11	11	9	9	8	8
8-14 days	42	42	32	25	24	23	21	21	20
15-21 days	54	54	54	48	38	37	35	32	31
22-33 days	291	291	291	291	284	273	258	245	234

FIGURE 2. Kaplan–Meier curves, by conversion group, of time to discontinuation during the first 8 weeks of brexpiprazole treatment (a) due to all reasons other than sponsor terminated study; (b) due to lack of efficacy; and (c) due to adverse events. Data for patients who received at least 1 dose of brexpiprazole in the conversion phase.

measured by the time from randomization to impending relapse] was demonstrated at a prespecified interim analysis [conducted after 45 events of impending relapse], and so the trial was terminated early);¹³ (b) due to lack of efficacy; and (c) due to adverse events.

Overall, discontinuation rates due to lack of efficacy and due to adverse events were low, regardless of time spent in the conversion phase.

In total, 292 (72.3%) of the 404 patients were converted to brexpiprazole and completed 8 weeks. Fifty-four patients (13.4%) were converted to brexpiprazole but discontinued in <8 weeks, and 58 patients (14.4%) discontinued prior to converting to brexpiprazole. Of the 292 patients who completed 8 weeks of brexpiprazole treatment, most were converted to brexpiprazole over 22–33 days (80.1%), and fewer were converted over 1–7 days (2.4%), 8–14 days (6.5%), or 15–21 days (11.0%).

Reasons for discontinuation are given in Table 2. For patients who discontinued in <8 weeks, whether they converted to brexpiprazole or discontinued prior to converting, the most common reasons for discontinuation were that the patient withdrew consent and that the sponsor terminated the study early due to the positive results of the interim analysis.

Patient characteristics

As shown in Table 3, baseline demographics were comparable between patients who converted to brexpiprazole and completed 8 weeks and patients who discontinued in <8 weeks (converted or nonconverted). Regarding clinical characteristics, patients who discontinued in <8 weeks had a higher mean PANSS total score at baseline than patients who converted and completed 8 weeks (85.2 vs. 81.2).

Among patients who converted and completed 8 weeks, baseline demographic and clinical characteristics showed a number of inconsistencies between conversion groups, which should be considered in the context of the low number of patients in the 1–7 days (*n*=7) and 8–14 days (*n*=19) groups (Table 3). For example, the proportions of patients who were female or who were black were higher in the 1–7 day group (57.1% and 57.1%, respectively) than in the other conversion groups (21.9–41.9% and 17.5–26.3%, respectively). Furthermore, the 1–7 day group had less severe disease than the other conversion groups, as measured by PANSS total and Personal and Social Performance (PSP) scale total scores.

There were no notable differences in patient characteristics between conversion groups for patients who converted and completed 8 weeks and patients who discontinued in <8 weeks (data not shown).

Baseline concomitant antipsychotics by conversion group are listed in Table 4. There were no statistically significant differences between patients who converted to brexpiprazole and completed 8 weeks and patients who discontinued in <8 weeks (converted or nonconverted), in terms of the proportion of patients who

TABLE 2. Reasons for brexpiprazole treatment discontinuation, by conversion group, for patients who converted to brexpiprazole but discontinued in <8 weeks, and for patients who discontinued prior to converting to brexpiprazole^a

<i>n</i> (%)	Converted but discontinued in <8 weeks				Total (<i>n</i> = 54)
	1–7 days (<i>n</i> = 3)	8–14 days (<i>n</i> = 6)	15–21 days (<i>n</i> = 6)	22–33 days (<i>n</i> = 39)	
Discontinued	3 (100.0)	6 (100.0)	6 (100.0)	39 (100.0)	54 (100.0)
Patient withdrew consent	0 (0.0)	3 (50.0)	3 (50.0)	12 (30.8)	18 (33.3)
Sponsor terminated study early due to interim analysis	1 (33.3)	1 (16.7)	0 (0.0)	9 (23.1)	11 (20.4)
Adverse event	0 (0.0)	2 (33.3)	1 (16.7)	7 (17.9)	10 (18.5)
Patient met withdrawal criteria	0 (0.0)	0 (0.0)	1 (16.7)	6 (15.4)	7 (13.0)
Lack of efficacy	1 (33.3)	0 (0.0)	0 (0.0)	2 (5.1)	3 (5.6)
Withdrawn by the investigator	0 (0.0)	0 (0.0)	1 (16.7)	2 (5.1)	3 (5.6)
Lost to follow-up	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)

<i>n</i> (%)	Discontinued prior to converting				Total (<i>n</i> = 58)
	1–7 days (<i>n</i> = 7)	8–14 days (<i>n</i> = 17)	15–21 days (<i>n</i> = 16)	22–33 days (<i>n</i> = 18)	
Discontinued	7 (100.0)	17 (100.0)	16 (100.0)	18 (100.0)	58 (100.0)
Patient withdrew consent	2 (28.6)	4 (23.5)	4 (25.0)	6 (33.3)	16 (27.6)
Sponsor terminated study early due to interim analysis	3 (42.9)	7 (41.2)	6 (37.5)	3 (16.7)	19 (32.8)
Adverse event	1 (14.3)	2 (11.8)	3 (18.8)	2 (11.1)	8 (13.8)
Patient met withdrawal criteria	0 (0.0)	1 (5.9)	0 (0.0)	2 (11.1)	3 (5.2)
Lack of efficacy	0 (0.0)	3 (17.6)	1 (6.3)	3 (16.7)	7 (12.1)
Withdrawn by the investigator	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	2 (3.4)
Lost to follow-up	1 (14.3)	0 (0.0)	1 (6.3)	0 (0.0)	2 (3.4)
Protocol deviation	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.7)

^a Data for patients who received at least 1 dose of brexpiprazole in the conversion phase.

TABLE 3. Baseline demographic and clinical characteristics, by conversion group^a

	Total (<i>N</i> = 404)	Converted and completed 8 weeks				Total completed 8 weeks (<i>n</i> = 292)	Total discontinued in <8 weeks (<i>n</i> = 112)
		1–7 days (<i>n</i> = 7)	8–14 days (<i>n</i> = 19)	15–21 days (<i>n</i> = 32)	22–33 days (<i>n</i> = 234)		
Demographic characteristics							
Age (years), mean (SD)	39.8 (11.3)	39.4 (8.3)	39.2 (11.2)	42.2 (12.6)	39.7 (11.1)	40.0 (11.2)	39.2 (11.5)
BMI (kg/m ²), mean (SD)	27.4 (6.1)	28.9 (12.9)	27.5 (6.3)	26.8 (5.1)	27.5 (5.8)	27.5 (6.0)	27.3 (6.4)
Female, <i>n</i> (%)	160 (39.6)	4 (57.1)	6 (31.6)	7 (21.9)	98 (41.9)	115 (39.4)	45 (40.2)
Race, <i>n</i> (%)							
White	266 (65.8)	2 (28.6)	11 (57.9)	22 (68.8)	159 (67.9)	194 (66.4)	72 (64.3)
Black/African American	80 (19.8)	4 (57.1)	5 (26.3)	7 (21.9)	41 (17.5)	57 (19.5)	23 (20.5)
Asian	27 (6.7)	0 (0.0)	1 (5.3)	0 (0.0)	21 (9.0)	22 (7.5)	5 (4.5)
Other	31 (7.7)	1 (14.3)	2 (10.5)	3 (9.4)	13 (5.6)	19 (6.5)	12 (10.7)
Clinical characteristics							
Age at first diagnosis (years), mean (SD)	26.7 (8.7)	25.6 (6.0)	27.3 (10.8)	28.7 (10.6)	27.0 (8.1)	27.2 (8.5)	25.2 (8.8)
PANSS total score, mean (SD)	81.8 (11.5)	75.3 (11.0)	80.6 (11.4)	83.6 (10.0)	81.1 (12.2)	81.2 (11.9)	85.2 (8.5)
PANSS positive subscale score, mean (SD)	20.3 (4.3)	17.9 (3.5)	20.6 (4.1)	21.5 (3.9)	20.0 (4.4)	20.1 (4.3)	21.1 (4.6)
PANSS negative subscale score, mean (SD)	21.8 (4.6)	19.3 (4.0)	21.5 (4.3)	22.4 (3.3)	21.9 (4.9)	21.8 (4.7)	21.7 (4.3)
PANSS excited component score, mean (SD)	10.7 (3.4)	8.1 (1.9)	9.6 (3.1)	10.7 (3.1)	10.5 (3.3)	10.4 (3.3)	12.0 (3.4)
PSP total score, mean (SD)	47.2 (11.2)	64.3 (14.5)	41.9 (10.1)	47.7 (9.0)	46.6 (11.1)	46.9 (11.1)	48.0 (11.4)
	(<i>n</i> = 189)	(<i>n</i> = 3)	(<i>n</i> = 7)	(<i>n</i> = 18)	(<i>n</i> = 107)	(<i>n</i> = 135)	(<i>n</i> = 54)
CGI-S score, mean (SD)	4.2 (0.7)	4.0 (0.6)	4.2 (0.7)	4.2 (0.6)	4.1 (0.8)	4.1 (0.8)	4.3 (0.6)

BMI = body mass index; CGI-S = Clinical Global Impressions–Severity of illness; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance scale; SD = standard deviation.

^a Data for patients who received at least 1 dose of brexpiprazole in the conversion phase.

TABLE 4. Concomitant antipsychotics from which patients were switched to brexpiprazole during the conversion phase, by conversion group^a

Concomitant antipsychotics	Converted and completed 8 weeks							Total comparing the four conversion groups ^b (n = 292), n (%)	Total discontinued in <8 weeks (n = 112), n (%)	ρ value comparing total completed 8 weeks and total discontinued in <8 weeks ^b
	Total (N = 404), n (%)	1–7 days (n = 7), n (%)	8–14 days (n = 19), n (%)	15–21 days (n = 32), n (%)	22–33 days (n = 234), n (%)	ρ value comparing the four conversion groups ^b	Total completed 8 weeks (n = 292), n (%)			
Relatively strong antihistaminergic and/or anticholinergic properties	173 (42.8)	2 (28.6)	6 (31.6)	11 (34.4)	102 (43.6)	0.50	121 (41.4)	52 (46.4)	0.36	
Olanzapine	77 (19.1)	1 (14.3)	3 (15.8)	3 (9.4)	53 (22.6)		60 (20.5)	17 (15.2)		
Quetiapine ^c	73 (18.1)	1 (14.3)	3 (15.8)	4 (12.5)	39 (16.7)		47 (16.1)	26 (23.2)		
Chlorpromazine	25 (6.2)	0 (0.0)	0 (0.0)	3 (9.4)	11 (4.7)		14 (4.8)	11 (9.8)		
Clozapine	7 (1.7)	0 (0.0)	0 (0.0)	1 (3.1)	3 (1.3)		4 (1.4)	3 (2.7)		
Relatively strong antidopaminergic properties	283 (70.0)	5 (71.4)	12 (63.2)	25 (78.1)	163 (69.7)	0.69	205 (70.2)	78 (69.6)	0.91	
Risperidone	137 (33.9)	1 (14.3)	8 (42.1)	17 (53.1)	72 (30.8)		98 (33.6)	39 (34.8)		
Haloperidol	56 (13.9)	2 (28.6)	0 (0.0)	3 (9.4)	32 (13.7)		37 (12.7)	19 (17.0)		
Aripiprazole	44 (10.9)	2 (28.6)	3 (15.8)	4 (12.5)	25 (10.7)		34 (11.6)	10 (8.9)		
Trifluoperazine ^d	17 (4.2)	0 (0.0)	1 (5.3)	0 (0.0)	11 (4.7)		12 (4.1)	5 (4.5)		
Zucloperithiol ^e	17 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	11 (4.7)		11 (3.8)	6 (5.4)		
Amisulpride	16 (4.0)	0 (0.0)	0 (0.0)	1 (3.1)	11 (4.7)		12 (4.1)	4 (3.6)		
Chlorprothixene ^f	13 (3.2)	0 (0.0)	0 (0.0)	2 (6.3)	8 (3.4)		10 (3.4)	3 (2.7)		
Ziprasidone	8 (2.0)	0 (0.0)	0 (0.0)	1 (3.1)	6 (2.6)		7 (2.4)	1 (0.9)		
Fluphenazine ^g	8 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)		3 (1.0)	5 (4.5)		
Paliperidone	7 (1.7)	1 (14.3)	0 (0.0)	0 (0.0)	4 (1.7)		5 (1.7)	2 (1.8)		
Flupentixol	5 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)		3 (1.0)	2 (1.8)		
Perphenazine	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)		2 (0.7)	1 (0.9)		
Asenapine	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)		2 (0.7)	0 (0.0)		
Iloperidone	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)		1 (0.3)	1 (0.9)		
Long-acting injectable	11 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.8)	0.51	9 (3.1)	2 (1.8)	0.47	
Flupentixol decanoate	5 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.1)		5 (1.7)	0 (0.0)		
Haloperidol decanoate	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)		1 (0.3)	1 (0.9)		
Paliperidone palmitate	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)		1 (0.3)	1 (0.9)		
Fluphenazine enanthate	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)		1 (0.3)	0 (0.0)		
Zucloperithiol decanoate	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)		1 (0.3)	0 (0.0)		
Unknown antipsychotic	7 (1.7)	0 (0.0)	1 (5.3)	0 (0.0)	4 (1.7)		5 (1.7)	2 (1.8)		

^a Data for patients who received at least 1 dose of brexpiprazole in the conversion phase. Patients may have received more than one concomitant antipsychotic. Antipsychotics are grouped according to their pharmacodynamic properties, as previously described⁸ or as defined by the authors.

^b ρ values were calculated using a chi-squared test.

^c Quetiapine or quetiapine fumarate.

^d Trifluoperazine or trifluoperazine hydrochloride.

^e Zucloperithiol, zucloperithiol acetate, or zucloperithiol hydrochloride.

^f Chlorprothixene or chlorprothixene hydrochloride.

^g Fluphenazine or fluphenazine hydrochloride.

switched from antipsychotics with relatively strong antihistaminergic/anticholinergic or antidopaminergic properties or long-acting injectable (LAI) antipsychotics.

Among patients who converted and completed 8 weeks, there were no statistically significant differences between conversion groups in terms of the proportion of patients who switched from antipsychotics with relatively strong antihistaminergic/anticholinergic or antidopaminergic properties (Table 4). Similar non-statistically significant differences between conversion groups were observed for patients who discontinued in <8 weeks (data not shown).

TEAEs

The incidence of TEAEs was comparable between the patients who converted to brexpiprazole and completed 8 weeks (49.7%) and the patients who discontinued in <8 weeks (converted or nonconverted) (47.3%), although the latter group, by definition, spent less time on brexpiprazole.

TEAEs with incidence $\geq 2.0\%$ during the first 8 weeks of brexpiprazole treatment are listed in Table 5 and Supplementary Table 1. Across all patients, the most common individual TEAEs (incidence $\geq 5\%$) were insomnia (11.1%), headache (7.2%), agitation (6.2%), and akathisia (5.2%).

Among patients who converted and completed 8 weeks, the incidence of TEAEs over 8 weeks was lower among those converted over 22–33 days (44.4%) than in the other conversion groups (62.5–84.2%).

Efficacy

Changes from baseline in PANSS total and CGI-S scores are presented in Table 6. Among patients who converted to brexpiprazole and completed 8 weeks, each conversion group showed improvements in PANSS total and CGI-S scores from baseline to stabilization phase weeks 4, 6, and 8. There were no statistically significant differences in the magnitude of improvement from baseline between the conversion groups.

Discussion

In this post hoc analysis of a long-term, controlled clinical study of brexpiprazole as maintenance treatment for schizophrenia, patients were converted from previous antipsychotic(s) to brexpiprazole monotherapy over a time period of 1–4 weeks, according to the investigators' judgment (and the protocol-defined washout of prohibited concomitant medications). The majority of patients who were successfully switched and completed 8 weeks of brexpiprazole treatment were converted from previous antipsychotic(s) to brexpiprazole monotherapy over a

TABLE 5. Treatment-emergent adverse events (TEAEs) in the 8 weeks from the start of the conversion phase (the first dose of brexpiprazole), by conversion group^a

n (%)	Total (N = 404)	Converted and completed 8 weeks				Total completed 8 weeks (n = 292)	Total discontinued in <8 weeks (n = 112)
		1–7 days (n = 7)	8–14 days (n = 19)	15–21 days (n = 32)	22–33 days (n = 234)		
Any TEAE	198 (49.0)	5 (71.4)	16 (84.2)	20 (62.5)	104 (44.4)	145 (49.7)	53 (47.3)
TEAEs with incidence $\geq 2.0\%$ in the "total completed 8 weeks" or "total discontinued in <8 weeks" groups							
Insomnia	45 (11.1)	2 (28.6)	3 (15.8)	7 (21.9)	27 (11.5)	39 (13.4)	6 (5.4)
Headache	29 (7.2)	1 (14.3)	3 (15.8)	2 (6.3)	14 (6.0)	20 (6.8)	9 (8.0)
Agitation	25 (6.2)	1 (14.3)	1 (5.3)	2 (6.3)	12 (5.1)	16 (5.5)	9 (8.0)
Akathisia	21 (5.2)	0 (0.0)	1 (5.3)	2 (6.3)	13 (5.6)	16 (5.5)	5 (4.5)
Nasopharyngitis	18 (4.5)	0 (0.0)	3 (15.8)	1 (3.1)	10 (4.3)	14 (4.8)	4 (3.6)
Nausea	13 (3.2)	0 (0.0)	1 (5.3)	1 (3.1)	7 (3.0)	9 (3.1)	4 (3.6)
Dizziness	10 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.4)	8 (2.7)	2 (1.8)
Tremor	10 (2.5)	0 (0.0)	0 (0.0)	2 (6.3)	4 (1.7)	6 (2.1)	4 (3.6)
Diarrhea	9 (2.2)	1 (14.3)	1 (5.3)	0 (0.0)	5 (2.1)	7 (2.4)	2 (1.8)
Schizophrenia	9 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.3)	8 (7.1)
Extrapyramidal disorder	8 (2.0)	0 (0.0)	1 (5.3)	2 (6.3)	5 (2.1)	8 (2.7)	0 (0.0)
Constipation	8 (2.0)	0 (0.0)	3 (15.8)	2 (6.3)	1 (0.4)	6 (2.1)	2 (1.8)
Vomiting	7 (1.7)	1 (14.3)	1 (5.3)	1 (3.1)	3 (1.3)	6 (2.1)	1 (0.9)
Abdominal discomfort	6 (1.5)	1 (14.3)	1 (5.3)	1 (3.1)	3 (1.3)	6 (2.1)	0 (0.0)
Upper respiratory tract infection	6 (1.5)	1 (14.3)	0 (0.0)	1 (3.1)	4 (1.7)	6 (2.1)	0 (0.0)

^a Data for patients who received at least 1 dose of brexpiprazole in the conversion phase.

TABLE 6. Change from baseline in PANSS total score and CGI-S score with brexpiprazole treatment, by conversion group^a

	Converted and completed 8 weeks				<i>p</i> value comparing the four conversion groups ^b
	1–7 days (<i>n</i> = 7)	8–14 days (<i>n</i> = 19)	15–21 days (<i>n</i> = 32)	22–33 days (<i>n</i> = 234)	
Mean (<i>SD</i>) PANSS total score at baseline	75.3 (11.0)	80.6 (11.4)	83.6 (10.0)	81.1 (12.2)	
Mean (<i>SD</i>) change in PANSS total score from baseline to:					
Stabilization phase week 4	–19.6 (11.2)	–21.6 (13.6)	–15.3 (6.6)	–17.5 (11.4) ^e	0.2557
Stabilization phase week 6	–18.6 (14.5)	–22.8 (13.9)	–17.0 (8.6) ^c	–19.2 (11.7) ^f	0.3932
Stabilization phase week 8	–21.3 (13.1)	–23.8 (17.1)	–19.6 (10.6) ^d	–20.6 (12.2) ^g	0.7012
Mean (<i>SD</i>) CGI-S score at baseline	4.0 (0.6)	4.2 (0.7)	4.2 (0.6)	4.1 (0.8)	
Mean (<i>SD</i>) change in CGI-S score from baseline to:					
Stabilization phase week 4	–1.0 (0.8)	–1.2 (0.8)	–0.8 (0.7)	–0.8 (0.8) ^e	0.1894
Stabilization phase week 6	–0.9 (0.7)	–1.3 (0.9)	–0.8 (0.7) ^c	–0.9 (0.8) ^f	0.3135
Stabilization phase week 8	–1.0 (0.8)	–1.3 (1.0)	–1.1 (0.7) ^d	–1.0 (0.8) ^g	0.3213

CGI-S = Clinical Global Impressions–Severity of illness; PANSS = Positive and Negative Syndrome Scale; *SD* = standard deviation.

^a Data for patients who received at least 8 weeks of brexpiprazole treatment.

^b *p* values were calculated using one-way analysis of variance.

^c *n* = 30.

^d *n* = 27.

^e *n* = 226.

^f *n* = 215.

^g *n* = 199.

period of 22–33 days. Regardless of the conversion schedule, the rates of discontinuation due to lack of efficacy or due to adverse events were low and showed only small differences. In other words, groups of patients with whom clinicians attempted conversion over shorter time periods were no more likely to discontinue than groups for whom conversion was attempted over longer time periods. It is unclear if clinicians used unmeasured patient characteristics to preselect patients in whom they attempted a shorter conversion schedule during the switch to brexpiprazole. Similarly, it remains unclear whether clinicians chose the conversion schedules *a priori*, or if they prolonged the conversion period in patients who experienced emergent symptoms or problems. There was a numerically higher incidence of TEAEs over 8 weeks among patients who converted to brexpiprazole over 1–7 days and 8–14 days than among those who converted over 22–33 days, but the low number of patients in these groups limits between-group interpretations.

Oral antipsychotics were cross-titrated over 1–4 weeks and, within the defined 1–4 week window, clinicians used their judgment regarding the up-titration of brexpiprazole and the down-titration of previous antipsychotic: there was no defined schedule for dose escalation of brexpiprazole, delay prior to discontinuation of previous antipsychotic, or rate of discontinuation of previous antipsychotic. LAI antipsychotics were stopped abruptly prior to brexpiprazole initiation, which, due to the long half-lives of LAIs, can be equated to cross-titration.^{18,19} Antipsychotic switching may be complicated by potential

pharmacodynamic and pharmacokinetic withdrawal and rebound phenomena when switching from a highly antihistaminergic/anticholinergic antipsychotic to a less antihistaminergic/anticholinergic antipsychotic, to a partial D₂ agonist from a full D₂ antagonist, or to an antipsychotic with a longer half-life from one with a shorter half-life.^{2,8} Because brexpiprazole is a D₂ partial agonist with minimal antihistaminergic/anticholinergic properties, investigators may have chosen longer conversion periods to avoid these potential withdrawal and rebound phenomena.^{8,10} In general, switching strategies with overlap between the two agents may be the most beneficial to avoid intra-switch worsening/complications. In clinical practice, however, a longitudinal study in the Netherlands showed that the majority of antipsychotics are switched abruptly.²⁰ Furthermore, an open-label study of switching to aripiprazole (another D₂ partial agonist) from other antipsychotics found no safety differences between abrupt switching and cross-titration.²¹

Prior studies have not always shown a difference between switching strategies,^{9,22,23} for reasons that may include the hospitalization status of patients, benzodiazepine use (often permitted but unmeasured) that could counter rebound phenomena, and the differing pharmacologic profiles of pre-switch antipsychotics. A meta-analysis of five randomized controlled studies comparing plateau cross-titration with nondelayed cross-titration in patients with schizophrenia found no statistically significant differences on any clinical outcomes, including discontinuation rate, psychopathology, extrapyramidal symptoms, and TEAEs.⁹ The individual randomized

controlled trials included in the meta-analysis also failed to show the superiority of either switching strategy.⁹ However, in the meta-analysis, data for all antipsychotics were pooled together, independent of their pharmacokinetic and pharmacodynamic properties, and the different pharmacologic properties of the baseline, pre-switch antipsychotics were similarly not considered, which may have obscured differences across switching strategies. While not reflecting real-world clinical practice, these inconclusive findings seem to indicate that it may be difficult to generalize switching approaches (each patient may require an individualized switching strategy) and that switching strategies may especially differ for switches between antipsychotics with similar versus different pharmacologic properties.⁸ The current meta-analyses on switching did not have sufficient power to adequately address this issue, and future studies are needed for clarification, particularly now that three different partial D₂ agonists are available for which switches from full D₂ antagonists would at least theoretically be complicated by an interaction between partial D₂ agonism and an upregulated D₂ receptor system.⁸

In the present analysis, the efficacy of brexpiprazole was similar in all conversion groups, as demonstrated by improvements from baseline to stabilization phase weeks 4, 6, and 8 in PANSS total and CGI-S scores. Because patients were cross-titrated from a wide variety of antipsychotic drugs, the improvements in PANSS total and CGI-S indicate that conversion to brexpiprazole may be efficacious for acutely ill patients (who received at least 8 weeks of brexpiprazole treatment) regardless of their prior therapy or the switching schedule.

Limitations of the present analysis include: (1) that the switching strategy/duration of overlap was the clinicians' choice and not randomized, yet this feature also increases the real-world applicability and generalizability of the findings; (2) the exploratory, post hoc nature of the analyses; (3) the low numbers of patients who were converted to brexpiprazole over 1–7 and 8–14 days, which mandates caution when interpreting the findings that improvements in efficacy appeared to be irrespective of conversion rate; (4) the multiplicity of baseline antipsychotics, precluding a more definitive assessment beyond pharmacologically similar subgroups of antipsychotics as to whether the switch from any specific antipsychotic with specific pharmacodynamic and pharmacokinetic properties would be more or less problematic/associated with withdrawal or rebound phenomena when switching to brexpiprazole; and (5) the lack of information from clinicians about the reasons for the switching strategy employed. Strengths of the study include the overall size of the study population; the structured study phases and assessments; and the real-world decision-making regarding the switching strategy employed (within the protocol-specified 1–4 week duration).

Conclusions

The results presented here provide a mostly clinically driven evidence base from which clinicians can choose a switching paradigm for patients initiating brexpiprazole that best meets their patients' needs. In general, for a successful switch entailing at least 8 weeks of brexpiprazole treatment, a longer switching period of 22–33 days was employed and was efficacious. Additional, real-world data on preferred and successful switching strategies could be helpful to inform clinicians' optimal use of brexpiprazole in patient subgroups when converting treatment from specific other antipsychotics.

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Supplementary materials

To view supplementary material for this article, please visit <https://doi.org/10.1017/S1092852918001086>

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