ORIGINAL RESEARCH

Notice of correction 3/12/2019: In Table 1, the following values have been corrected: the percentage of Black/African American subjects who received oral antipsychotics; the PSP total score standard deviation in the paliperidone palmitate group, and the PSP total score mean and standard deviation in the oral antipsychotic group. On page 558, in the "Adherence" paragraph, the percentage of subjects with a medication possession ratio greater than 80% when clinician-based "prescription" records were used to assess oral medication adherence has been corrected.

Real-World Outcomes of Paliperidone Palmitate Compared to Daily Oral Antipsychotic Therapy in Schizophrenia: A Randomized, Open-Label, Review Board–Blinded 15-Month Study

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ABSTRACT

Objective: The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study compared the effects of once-monthly paliperidone palmitate with daily oral antipsychotics on treatment failure in adults with schizophrenia.

Method: The PRIDE study is a 15-month, randomized, multicenter study (May 5, 2010, to December 9, 2013) of adult subjects with a *DSM-IV* diagnosis of schizophrenia and a history of incarceration. Subjects were randomly assigned to once-monthly paliperidone palmitate injections or daily oral antipsychotics (randomly assigned from 7 acceptable, prespecified oral antipsychotics) for 15 months. The primary end point was time to first treatment failure, defined as arrest/incarceration; psychiatric hospitalization; suicide; treatment discontinuation or supplementation due to inadequate efficacy, safety, or tolerability; or increased psychiatric services to prevent hospitalization. Time to first treatment failure was determined by a blinded event-monitoring board and analyzed with the Kaplan-Meier method.

Results: In this study, 450 patients were randomly assigned, and 444 were included in the intent-to-treat population. Paliperidone palmitate was associated with significant delay in time to first treatment failure versus oral antipsychotics (hazard ratio, 1.43; 95% CI, 1.09–1.88; log rank $P = .011$). Observed treatment failure rates over 15 months were 39.8% and 53.7%, respectively. Arrest/incarceration and psychiatric hospitalization were the most common reasons for treatment failure in the paliperidone palmitate and oral antipsychotic groups (21.2% vs 29.4% and 8.0% vs 11.9%, respectively). The 5 most common treatment-emergent adverse events for the paliperidone palmitate treatment group were injection site pain (18.6% of subjects), insomnia (16.8%), weight increased (11.9%), akathisia (11.1%), and anxiety (10.6%).

Conclusions: In a trial designed to reflect real-world management of schizophrenia, once-monthly paliperidone palmitate demonstrated superiority compared to oral antipsychotics in delaying time to treatment failure.

Trial Registration: Clinicaltrials.gov Identifier: NCT01157351

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Schizophrenia is a serious chronic mental illness characterized by hallucinations, delusions, and significant functional disabilities that affects approximately 1.1% of adults in the United States.[1,2] Schizophrenia places a large economic burden on the health care system, resulting in estimated direct annual medical costs of $43 to $58 billion[3] and a significant societal impact in terms of overall health care burden.[4]

For individuals with schizophrenia to fulfill their potential and lead more meaningful lives their real-world treatment needs must be better understood and addressed. At present, effective management of schizophrenia is complicated by a variety of factors, including contacts with the criminal justice system, multiple hospitalizations, comorbid substance abuse, challenges to treatment adherence, unemployment, and unstable living conditions.[5–7] Most clinical trials select for individuals who are not broadly representative of patients from these real-world settings,[8–10] limiting the generalizability of their results. Their broad applicability is further complicated by the frequent choice of scale-based rather than clinically defined end points.[11,12] A consequence of such designs is that they fail to evaluate many of the complex issues associated with the daily management of schizophrenia.

Poor treatment adherence is common among individuals with schizophrenia, particularly in patients with prior involvement with the criminal justice system or comorbid substance abuse.[6,13,14] Such problems with adherence is frequently a precursor to cycles of relapse and recidivism. Long-acting injectable (LAI) antipsychotic therapies can deliver therapeutic concentrations continuously over several weeks and eliminate the need for daily medication administration.[15] Further, their mode of administration provides physicians with certain knowledge of adherence. As a result, use of LAI antipsychotic therapy may facilitate continuity of treatment and support better outcomes. Despite these apparent advantages, clinical trials comparing LAI and oral antipsychotics have produced inconsistent results.[16–21] We hypothesize that the inconsistencies in these reports might be a consequence of the study designs chosen for these comparisons and, possibly, a failure to follow a broad spectrum of patients using measures that reflect an adequate breadth of real-world outcomes.[22] We describe a study, Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE), that compares once-monthly paliperidone palmitate with daily oral antipsychotics in patients with schizophrenia who are at risk for relapse. The study was designed to reflect real-world management of schizophrenia, as defined by the patients included, and clinically meaningful outcome measures.

Clinical Points

- Most randomized clinical trials do not enroll patients with complex comorbidities/histories; thus, these trials may not broadly reflect important treatment considerations for persons with schizophrenia.
- The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study was designed to reflect real-world treatment of schizophrenia, as defined by patient selection, treatment approaches, and clinically meaningful outcomes.
- The PRIDE study results demonstrate that, by using a design reflecting real-world considerations, once-monthly treatment with paliperidone palmitate was more effective in delaying treatment failure than treatment with daily oral antipsychotics.

METHOD

Study Design

The PRIDE study is a randomized, prospective, open-label, event-monitoring board–blinded, parallel-group study that compared paliperidone palmitate and oral antipsychotics on treatment failure in subjects with schizophrenia. The study incorporated both explanatory (efficacy) and pragmatic (effectiveness) design elements, allowing documentation of efficacy and effectiveness outcomes. Conducted between May 5, 2010, and December 9, 2013, the study included a screening phase of up to 2 weeks, followed by a 15-month randomized, open-label treatment phase. It was registered on ClinicalTrials.gov (identifier: NCT01157351). More complete details of the study design have been previously published.[23]

Participants

Participants were enrolled from 50 sites across 25 US states and Puerto Rico. To enhance enrollment of subjects often excluded from trials, efforts were made to recruit subjects from nontraditional locations, such as homeless shelters, soup kitchens, and jail-release or diversion programs. The study's major inclusion criteria enlisted adults aged 18 to 65 years with a current diagnosis of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [*DSM-IV*] criteria[24] that was confirmed by the Mini-International Neuropsychiatric Interview [MINI], version 6.0[25]). Subjects must have been taken into custody by the criminal justice system ≥2 times in the previous 2 years, with ≥1 of these events leading to incarceration; released from most recent custody within 90 days of the screening visit; and accepting of a once-monthly, LAI antipsychotic. To maximize study retention, subjects designated a reliable external contact (eg, family member, case manager). Major exclusion criteria included use of either clozapine within 3 months of screening or an injectable antipsychotic within 2 injection cycles of screening. Substance abuse was not exclusionary, but subjects who had abused intravenous drugs within 3 months of screening or had an opiate dependence disorder (*DSM-IV*) were excluded. The study was approved by each site's institutional review board and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Interventions

Before random treatment assignment, clinicians, together with each subject, reviewed the 7 oral antipsychotics available in this study (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone) to determine their acceptability based on prior experience. Up to 6 medications could be deselected by the participant or physician.

Randomization

To reduce treatment selection bias, an equipoise-stratified randomization scheme[26] was used for treatment assignment and implemented via an interactive voice response system. Subjects with the same oral antipsychotic selections were placed in the same randomization strata and assigned in a 1:1 ratio to treatment with flexibly dosed paliperidone palmitate (78–234 mg) or a flexibly dosed oral antipsychotic. For subjects assigned to the oral antipsychotics arm, the specific agent was randomly selected from the group of prespecified, acceptable oral antipsychotics. Any oral antipsychotic prescribed before randomization was tapered and discontinued over the first 8 days after randomization. Paliperidone palmitate injection was administered by staff at the clinical site. Patients randomized to oral antipsychotics received a prescription and a voucher to cover its cost. Prescriptions were filled at a local pharmacy.

Study Medications

Subjects assigned to the paliperidone palmitate group were initiated with 2 injections in the deltoid muscle that were given approximately 1 week apart: 234 mg on day 1 and 156 mg on day 8 (±4 days). Flexible monthly maintenance doses of paliperidone palmitate within a range of 78–234 mg (50–150 mg equivalents; recommended target maintenance dose was 156 mg) were started on day 38. Doses of oral antipsychotic monotherapy were selected and adjusted within the dose range of the package insert (occasional dosing outside of package insert range was allowed). Nonantipsychotic psychotropic medications (ie, mood stabilizers, antidepressants, anxiolytics, or hypnotics) were allowed.

Clinical Assessments and Outcome Measure

Throughout the 15-month treatment period, study visits occurred on days 8 (±4), 15 (±3), and 38 (±7), and monthly thereafter (every 30 [±7] days). Subjects were assessed at each visit for treatment failure. Subjects were encouraged to continue in the study to their predefined, 15-month end-of-observation date, regardless of early discontinuation of their randomized treatment assignment or achievement of the primary end point. A subject was considered to be a completer for the efficacy analysis if he or she either experienced a treatment failure event or completed the 15-month study follow-up.

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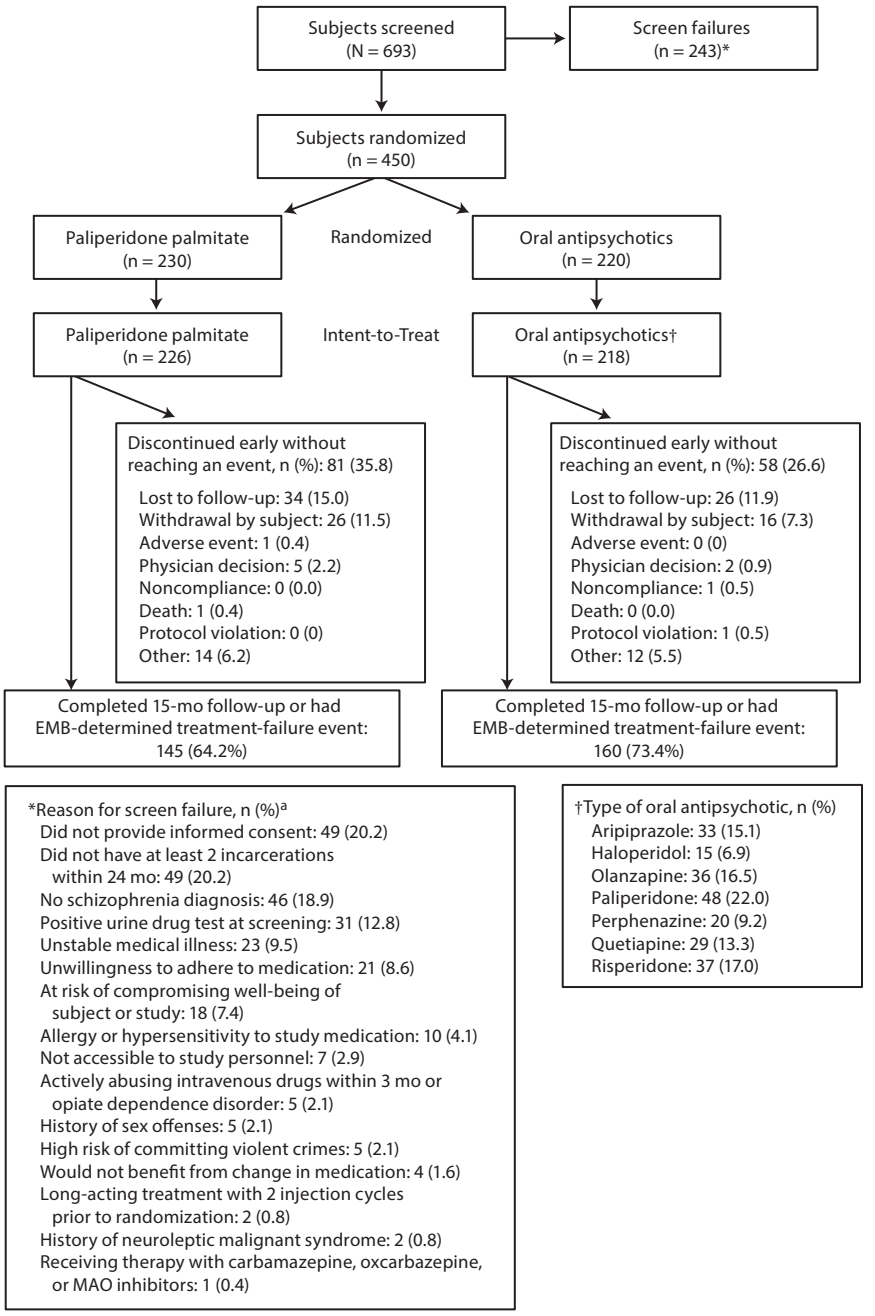
The primary study end point was time to first treatment failure, as determined by an independent event-monitoring board that was blinded to individual subject treatment assignment. Treatment failure was defined as 1 of the following: arrest/incarceration, psychiatric hospitalization, suicide, discontinuation of antipsychotic treatment due to inadequate efficacy, treatment supplementation with another antipsychotic due to inadequate efficacy, discontinuation of antipsychotic treatment due to safety or tolerability concerns, or an increase in the level of psychiatric services to prevent imminent psychiatric hospitalization.

Prespecified key secondary efficacy end points listed in order of priority were time to first psychiatric hospitalization or arrest/incarceration, change in Personal and Social Performance Scale (PSP) scores, time to first psychiatric hospitalization, and change in Clinical Global Impressions-Severity of Illness scale (CGI-S) score. Safety assessments included monitoring of adverse events (AEs), vital signs, physical examinations, and clinical laboratory tests.

Figure 1. Study Flow



[a]Percentages based on total number of screen failures (n = 243). Screen failures could be due to more than 1 reason.
Abbreviations: EMB = Event Monitoring Board, MAO = monoamine oxidase.

Sample Size

Sample size estimation was based on testing treatment group differences measured by hazard ratio (HR), using a 2-sided exponential maximum likelihood test at a .05 significance level. Detecting an HR (treatment/control) of 0.516 with 80% power requires a total of at least 72 treatment failure events. Assuming 30% of randomized subjects would drop out of the study before experiencing a treatment failure event, a total of 442 subjects (221 per group) would need to be randomized to achieve the required number of treatment failure events.

Statistical Analysis

The intent-to-treat (ITT) population, defined as all randomly assigned subjects who received ≥ 1 dose of their study treatment, was used for efficacy and safety analysis. To determine the relative effects of assigned treatments, an explanatory approach was used to assess the primary, key secondary, and safety end points. Primary and secondary analyses included all data from randomization until the end of randomly assigned treatment (28 days after the last injection of paliperidone palmitate or 1 day after the last dose of oral antipsychotic).

Demographic and baseline characteristics and AEs were summarized using descriptive statistics. Event-free probabilities of treatment failure and components of treatment failure were estimated by the Kaplan-Meier method. Treatment differences were compared using a log rank test. The HR and 95% confidence interval (CI) were estimated using a Cox proportional hazards model, with treatment as a fixed factor. Statistical significance was based on a 2-sided α of .05. A mixed-model repeated-measures analysis of covariance, using an unstructured covariance matrix

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with terms for treatment, time, treatment-by-time interaction, and baseline score, compared PSP total scores and CGI-S scores. To preserve the overall type I error rate at the 2-sided .05 significance level, the primary and key secondary hypotheses were tested using a fixed sequence gatekeeper approach. The hierarchy of the procedure was to test the primary hypothesis first at the .05 significance level, then to test the key secondary hypothesis at the .05 significance level. At each step, if the null hypothesis failed to be rejected ($P \geq .05$), formal testing would be terminated and current and all subsequent null hypotheses would not be rejected. Testing of subsequent hypotheses continued, but the results were considered exploratory. All analyses were performed using SAS version 9.2 (SAS Institute Inc; Cary, North Carolina).

RESULTS

Patient Disposition and Baseline Characteristics

In this study, 693 subjects were screened, and 450 were randomly assigned (230 to paliperidone palmitate and 220 to oral antipsychotics; Figure 1); 444 subjects were included in the ITT population (paliperidone palmitate, n = 226; oral antipsychotics, n = 218). Overall, 305 subjects (68.7%) either had an event-monitoring board–identified treatment failure event or completed the 15-month study; 60 subjects (13.5%) were lost to follow-up, and 42 (9.5%) withdrew consent (Figure 1).

Baseline demographics and clinical characteristics did not differ significantly between arms (Table 1). Most subjects were male (86.3%) and black/African American (62.1%). The mean (SD) age was 38.1 (10.5) years, and the mean (SD) time since release from last incarceration was 42.2 (51.7) days. The majority of arrests prior to enrollment in the study were for nonviolent or drug offenses; 54.2%, 37.8%, and 29.1% of subjects were previously arrested due to felonies, misdemeanors, or infractions, respectively. It should be noted that definitions for arrest-type classifications vary by jurisdiction. A total of 59.5% of subjects had comorbid substance abuse. Additionally, 16.1% of the oral antipsychotic group had been taking their randomly selected medication within 7 days of randomization. For the paliperidone palmitate group, 22.6% had been taking either paliperidone or risperidone within 7 days of randomization. Overall, 74.3% in the paliperidone palmitate treatment arm and 80.3% in the oral antipsychotic treatment arm used ≥ 1 concomitant psychotropic medication (including antipsychotics) during the study (see eTable 1 at PSYCHIATRIST.COM). Frequently used concomitant nonantipsychotic psychotropic medications for paliperidone palmitate versus oral antipsychotic groups included antidepressants (37.2% vs 41.3%), benzodiazepines (19.9% vs 22.5%), mood stabilizers/antiepileptics (17.3% vs 17.0%), and nonbenzodiazepine hypnotics/anxiolytics (14.6% vs 10.6%) (eTable 1).

Table 1. Demographic and Baseline Characteristics (intent-to-treat population)

Characteristic	Paliperidone Palmitate (n = 226)	Oral Antipsychotics (n = 218)
Age, mean (SD), y	37.7 (10.6)	38.6 (10.4)
Male, n (%)	193 (85.4)	190 (87.2)
Race, n (%)	(n = 226)	(n = 217)
White	73 (32.3)	74 (34.1)
Black/African American	145 (64.2)	130 (59.9)
Other	8 (3.5)	13 (6.0)
Ethnicity, n (%)	(n = 216)	(n = 212)
Hispanic or Latino	31 (14.4)	36 (17.0)
Not Hispanic or Latino	185 (85.6)	176 (83.0)
BMI (kg/m^2), mean (SD)	(n = 225) 27.9 (5.6)	(n = 218) 27.8 (5.0)
Time since release from the last incarceration, mean (SD), d	(n = 226) 38.9 (50.3)	(n = 217) 45.7 (53.0)
Duration of illness, n (%)	(n = 226)	(n = 216)
≤ 5 y	42 (18.6)	35 (16.2)
> 5 y	184 (81.4)	181 (83.8)
No. of psychiatric hospitalizations in lifetime, mean (SD)	(n = 176) 7.3 (16.4)	(n = 170) 5.7 (5.6)
No. of psychiatric hospitalizations in the past 12 mo, mean (SD)	(n = 176) 1.3 (7.6)	(n = 173) 1.0 (1.5)
Concurrent substance abuse (including alcohol), n (%)	130 (57.5)	134 (61.5)
Type of arrest, n (%)		
Infraction[a]	68 (30.1)	61 (28.0)
Most common (≥ 10%, either group)		
Violation of probation/parole	44 (19.5)	39 (17.9)
Misdemeanor[b]	90 (39.8)	78 (35.8)
Most common (≥ 10%, either group)		
Vagrancy, public intoxication	26 (11.5)	26 (11.9)
Felony[c]	108 (47.8)	128 (58.7)
Most common (≥ 10%, either group)		
Drug charges	34 (15.0)	40 (18.3)
Assault (private citizen)	24 (10.6)	28 (12.8)
Burglary/larceny/breaking and entering	16 (7.1)	22 (10.1)
Homelessness,[d] n (%)	(n = 221) 28 (12.7)	(n = 210) 34 (16.2)
PSP total score, mean (SD)	(n = 226) 54.8 (12.8)	(n = 215) 55.0 (12.7)
CGI-S score, mean (SD)	(n = 226) 3.8 (0.8)	(n = 217) 3.9 (0.7)

[a]Infractions are defined as a violation of a rule, ordinance, or regulation. They are considered minor crimes and are sometimes called petty crimes or summary offenses. They are punishable usually by a fine, rather than jail time; typically, these are local crimes related to traffic, parking, or noise violations.
[b]Misdemeanors are defined as lesser crimes (ie, do not rise to severity of a felony). Misdemeanors are considered crimes of low seriousness.
[c]Felonies are defined as the most serious classification of crimes. Both property crimes and person crimes are considered felonies. Persons committing the crime, as well as anyone who aided and abetted the felon before the crime, during the crime, or as an accessory to the crime after it was committed, can be charged with a felony.
[d]Homelessness is defined as living on the streets or in an emergency shelter for the homeless since the time of release from jail.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness, PSP = Personal Social Performance Scale.

Primary Outcome: First Treatment Failure

Ninety subjects (39.8%) in the paliperidone palmitate group and 117 subjects (53.7%) in the oral antipsychotic group had a treatment failure event. Paliperidone palmitate was superior to oral antipsychotics in delaying time to first treatment failure (HR, 1.43; 95% CI, 1.09–1.88; $P = .011$) (Figure 2). Median times to first treatment failure were 416 and 226 days in the paliperidone palmitate and oral antipsychotic groups, respectively. The most common

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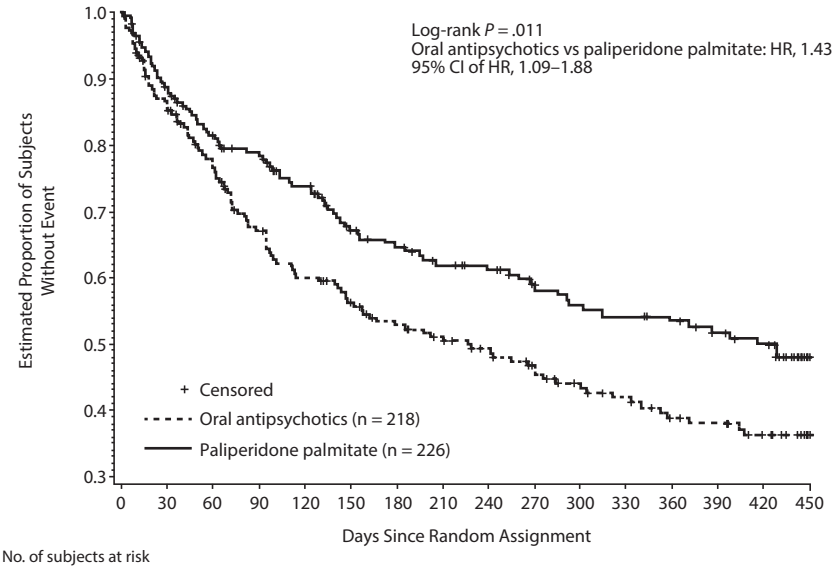
Figure 2. Kaplan-Meier Estimate of Time to First Treatment Failure (A) and Reasons for Treatment Failure (B)[a]

A. Time to First Treatment Failure



No. of subjects at risk

Oral antipsychotics	218	183	152	126	112	102	92	86	79	71	61	58	49	47	41	29
Paliperidone palmitate	226	190	162	148	128	107	100	92	88	76	70	68	65	60	56	31

B. Reason for First Treatment Failure

Reason	Paliperidone Palmitate (n = 226), n (%)	Oral Antipsychotics (n = 218), n (%)
Any	90 (39.8)	117 (53.7)
Arrest/incarceration	48 (21.2)	64 (29.4)
Psychiatric hospitalization	18 (8.0)	26 (11.9)
Discontinuation of antipsychotic treatment due to safety or tolerability	15 (6.6)	8 (3.7)
Treatment supplementation with another antipsychotic due to inadequate efficacy	5 (2.2)	6 (2.8)
Discontinuation of antipsychotic treatment due to inadequate efficacy	1 (0.4)	9 (4.1)
Increase in level of psychiatric services to prevent imminent psychiatric hospitalization	3 (1.3)	4 (1.8)
Suicide	0	0

[a]Data from randomization until end of randomly assigned treatment (28 days after last injection of paliperidone palmitate or 1 day after last dose of oral antipsychotic).
Abbreviation: HR = hazard ratio.

reasons for first treatment failure were arrest/incarceration (21.2% vs 29.4%) and psychiatric hospitalization (8.0% vs 11.9%) (Figure 2). No suicides were reported.

Secondary Outcomes

Time to first psychiatric hospitalization or arrest/incarceration. Seventy-six subjects (33.6%) in the paliperidone palmitate group and 98 subjects (45.0%) in the oral antipsychotic group had a psychiatric hospitalization or arrest/incarceration as a first treatment failure event. Paliperidone palmitate was superior to oral antipsychotics in delaying time to first psychiatric hospitalization or arrest/incarceration (HR, 1.43; 95% CI, 1.06–1.93; $P = .019$) (Figure 3). Median time to first psychiatric hospitalization or arrest/incarceration was not reached in the paliperidone palmitate group (> 450 days) and was 274 days in the oral antipsychotic group.

Personal and Social Performance Scale. No significant between-group differences were observed in mean change in PSP total scores (least squares mean [standard error (SE)] difference = 0.39 [0.98]; $P = .689$). Subsequent analyses of other secondary efficacy variables were considered exploratory.

CGI-S. No significant between-group differences were observed in mean change in CGI-S scores (least squares mean [SE] difference = –0.06 [0.05]; nominal $P = .296$).

First psychiatric hospitalization and first arrest/incarceration. No significant difference in time to first psychiatric hospitalization was seen between the paliperidone palmitate and oral antipsychotic groups (HR, 1.19; 95% CI, 0.67–2.11; nominal $P = .552$). In contrast, paliperidone palmitate was superior to oral antipsychotics in delaying time to first arrest/incarceration (HR, 1.49; 95% CI, 1.08–2.06; nominal $P = .016$).

Adherence. When injection records were used to assess adherence, 95.2% in the paliperidone palmitate group had a medication possession ratio (MPR) > 80%. When clinician-based "prescription" records were used to assess oral medication adherence, 78.6% had an MPR > 80%. When pharmacy-based "refill" prescription records were used to assess oral medication adherence, 24.3% in the oral group had an MPR > 80%.

Exposure to study medication. Mean (SD) exposure to paliperidone palmitate was 266.2 (174.5) days, and mean exposure to oral antipsychotics was 271.5 (178.5) days. Doses are summarized in eTable 2. Additionally, the mean and median number of injections received by paliperidone palmitate patients was generally comparable to the mean and median number of prescriptions received by patients in the oral antipsychotic group (eTable 2).

Safety. Treatment-emergent AEs (TEAEs) were reported in 85.8% and 79.8% of subjects in the paliperidone palmitate and oral antipsychotic treatment arms, respectively. Most common were injection site pain (18.6% of subjects), insomnia (16.8%), weight increase (11.9%), akathisia (11.1%), and anxiety (10.6%) in the paliperidone palmitate group and insomnia (11.5%), headache (8.3%), dry mouth (8.3%), anxiety (7.3%), and sedation (7.3%) in the oral antipsychotic group (Table 2). Incidence of serious TEAEs was 17.3% and 21.6% in the paliperidone palmitate and oral antipsychotic groups, respectively. Treatment-emergent AEs leading to study drug discontinuation occurred in 11.9% of paliperidone palmitate and 7.8% of oral antipsychotic subjects (eTable 3). Rates of extrapyramidal symptom-related TEAEs

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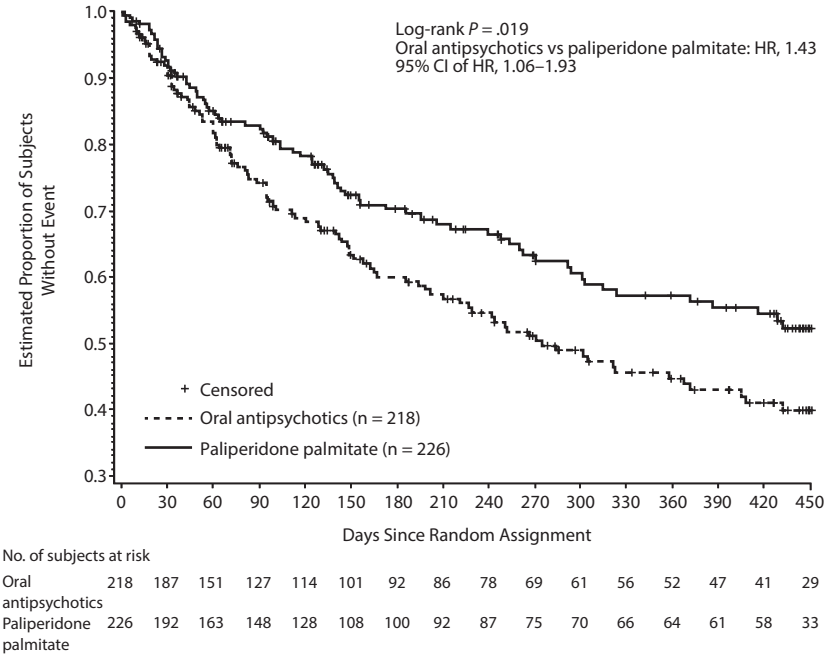
Figure 3. Kaplan-Meier Estimate of Time to First Psychiatric Hospitalization or Arrest/Incarceration[a]



No. of subjects at risk

Oral antipsychotics	218	187	151	127	114	101	92	86	78	69	61	56	52	47	41	29
Paliperidone palmitate	226	192	163	148	128	108	100	92	87	75	70	66	64	61	58	33

[a]Data from randomization until end of randomly assigned treatment (28 days after last injection of paliperidone palmitate or 1 day after last dose of oral antipsychotic).
Abbreviation: HR = hazard ratio.

Table 2. Summary of Treatment-Emergent Adverse Events (TEAEs) in ≥ 5% of Subjects by Preferred Term[a,b]

TEAE, n (%)	Paliperidone Palmitate (n = 226)	Oral Antipsychotics (n = 218)
Any	194 (85.8)	174 (79.8)
Injection site pain	42 (18.6)	0
Insomnia	38 (16.8)	25 (11.5)
Weight increased	27 (11.9)	13 (6.0)
Akathisia	25 (11.1)	15 (6.9)
Anxiety	24 (10.6)	16 (7.3)
Depression	17 (7.5)	14 (6.4)
Fatigue	17 (7.5)	6 (2.8)
Erectile dysfunction	17 (7.5)	0
Sedation	15 (6.6)	16 (7.3)
Dry mouth	15 (6.6)	18 (8.3)
Increased appetite	15 (6.6)	8 (3.7)
Nasopharyngitis	15 (6.6)	12 (5.5)
Headache	14 (6.2)	18 (8.3)
Libido decreased	13 (5.8)	3 (1.4)
Upper respiratory tract infection	13 (5.8)	10 (4.6)
Back pain	13 (5.8)	8 (3.7)
Schizophrenia	10 (4.4)	15 (6.9)
Somnolence	10 (4.4)	15 (6.9)
Toothache	10 (4.4)	12 (5.5)
Dizziness	5 (2.2)	11 (5.0)
Suicidal ideation	8 (3.5)	13 (6.0)

[a]Preferred terms of adverse events were based on version 12.0 of the Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddra.org).
[b]This table comprises data from randomization until the end of randomly assigned treatment (28 days after the last injection of paliperidone palmitate or 1 day after the last dose of oral antipsychotic).

for paliperidone palmitate versus oral antipsychotics were akathisia (11.1% vs 6.9%), dyskinesia (2.7% vs 1.4%), dystonia (2.2% vs 2.8%), and Parkinsonism (1.8% vs 1.8%). Incidence of prolactin-related TEAEs was 23.5% and 4.1% in the paliperidone palmitate and oral antipsychotic groups, respectively. Incidences of prolactin-related AEs by gender are presented in eTable 4. In all, 32.4% of subjects in the paliperidone palmitate group and 14.4% in the oral antipsychotic group had a ≥ 7% increase in weight. One death occurred in the paliperidone palmitate group and was considered by the investigator as unlikely related to the study drug. There were no unexpected safety concerns related to vital signs, physical examination findings, or clinical laboratory test results.

DISCUSSION

The PRIDE study demonstrated the superiority of once-monthly paliperidone palmitate over daily oral antipsychotics in delaying time to treatment failure in an innovative randomized study that reflects real-world management of schizophrenia. The study's premise that clinical trials with more pragmatic designs are more likely to demonstrate advantages of LAIs over oral antipsychotics was supported.[19–21] To increase the pragmatic focus of the study, persons at high risk for treatment nonadherence (ie, those with recent involvement with the criminal justice system, comorbid substance abuse, or unstable living conditions) were enrolled. In addition, considerable flexibility in treatment/management decisions by physicians and patients was allowed. Finally, objective and clinically relevant outcome measures were chosen as primary end points. The robust results favoring paliperidone palmitate over oral formulations of commonly used antipsychotics in delaying time to treatment failure suggest that these design differences may be relevant for demonstrating these treatment differences.

In the United States, the criminal justice system has become a frequent setting for management of patients with severe mental illness. It has overtaken psychiatric hospitals as a site for their institutionalization.[27] The results of the PRIDE study suggest that outcomes for this vulnerable population can be improved by medication choice. Indeed, outcomes of particular public health and economic importance (ie, arrest, incarceration, and hospitalization) were the most commonly observed primary end points in this study. We speculate that treatment with paliperidone palmitate leads to more consistent treatment exposure, resulting in fewer symptoms that lead to treatment failure.

Patient symptoms and functioning as measured by the CGI-S and PSP failed to demonstrate differences between paliperidone palmitate and oral treatments in this study. Although these findings may be correct, this failure may also be a consequence of ascertainment bias. That is, assessment with the CGI-S and PSP was not possible when subjects were institutionalized, points at which symptoms and functioning would likely be most deviant from baseline. On the other hand, when subjects were available for assessment, they were most likely to have improved, as evidenced by their ability to keep their clinic visit.

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The risk of reinstitutionalization in individuals with mental illness and contact with the criminal justice system is high.[28–30] Data from studies conducted in subjects with significant exposure to the criminal justice system reported rehospitalization rates up to 48% and reincarceration rate up to 68%.[28–30] In the PRIDE study, reinstitutionalization (ie, arrest/incarceration and hospitalization) rates were 33.6% for the paliperidone palmitate arm versus 45% for the oral antipsychotic arm. The lower reinstitutionalization rate observed in the PRIDE study suggests that paliperidone palmitate may reduce the risk of reinstitutionalization in this high-risk population.

In this study, neither patients nor clinicians were blinded to treatment assignment, but all primary end points were independently identified by a blinded event-monitoring board that had no knowledge of treatment assignment. Furthermore, the majority of the end points defined as treatment failures, such as incarceration and psychiatric hospitalization, were highly objective and were chosen for this study because they may indicate deterioration in the subject's clinical state. Although some outcomes such as discontinuation due to efficacy or safety may have been influenced by the knowledge of treatment assignment, they represented only approximately 10% of the treatment failures identified by the blinded event-monitoring board.

Paliperidone palmitate treatment was associated with numerically greater AEs, such as prolactin elevations, sexual side effects, and weight gain. This study was not powered or designed to detect differences from 7 individual oral antipsychotics. Given the varied safety profiles among these agents, the pooled data may have obscured tolerability issues relative to any individual oral agent.

The study was designed to reproduce 2 clinical management practices commonly experienced by patients with chronic schizophrenia: clinical visits where patients receive an LAI antipsychotic and visits where patients receive a prescription for an oral antipsychotic, which they fill in an outside pharmacy. In actual practice, treatment with oral antipsychotic medications requires multiple points of adherence. These include whether a clinic visit is made, whether a prescription is received, whether the prescription is filled, and, finally, whether the medication is taken as prescribed. For injectable medications, these requirements are limited to whether the patient attends a clinic visit and receives an injection. In this study, there was indirect assessment of adherence to medications. Study visits, prescriptions written, and injections were carefully documented. In addition, vouchers provided to pay for subjects' prescriptions when filled were also meant to serve as a record of this fulfillment. However, under the real-world conditions that existed for this study, other mechanisms for payment were potentially available. This led to a possible underestimation of medication possession. For these reasons, more reliable estimates of adherence were available for injectable than oral medications. In summary, the number of study visits was similar for subjects receiving oral medications and paliperidone palmitate, and the overall duration of exposure was comparable between the 2 groups; however, it was uncertain how many prescriptions were filled for the oral group and whether these patients took their medications as prescribed.

The study design retained some biases that may affect generalization of results. Subjects who were not willing to receive LAI therapy would not have enrolled. This may have contributed to a nonrandom selection process. Other notable differences in gender and race from the US population of persons with schizophrenia are also apparent.

CONCLUSIONS

The PRIDE study results demonstrated that once-monthly treatment with paliperidone palmitate was more effective in delaying treatment failure versus daily oral antipsychotics (median difference of 190 days) in a trial designed to reflect the real-world management of schizophrenia subjects at risk for treatment failure. These findings support the value of real-world study designs when attempting to identify treatment differences that may relate to formulation differences.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa and others), paliperidone (Invega), paliperidone palmitate (Invega Sustenna), quetiapine (Seroquel and others), risperidone (Risperdal and others).

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Supplementary Material

Article Title: Real-World Outcomes of Paliperidone Palmitate Compared to Daily Oral Antipsychotic Therapy in Schizophrenia: A Randomized, Open-Label, Review Board–Blinded 15-Month Study

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List of Supplementary Material for the article

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Online-only material

eTable 1. Concomitant Use of Psychotropic Medications (ITT population)

Psychotropic medication, No. (%)	Paliperidone Palmitate (n = 226)	Oral Antipsychotics (n = 218)
Any	168 (74.3)	175 (80.3)
Atypical antipsychotics	100 (44.2)	111 (50.9)
Antidepressants	84 (37.2)	90 (41.3)
Benzodiazepines	45 (19.9)	49 (22.5)
Antihistamines	45 (19.9)	55 (25.2)
Antiextrapyramidal symptoms	52 (23.0)	42 (19.3)
Mood stabilizers and antiepileptics	39 (17.3)	37 (17.0)
Nonbenzodiazepine hypnotics and anxiolytics	33 (14.6)	23 (10.6)
Beta blockers	33 (14.6)	27 (12.4)
Typical antipsychotics	25 (11.1)	28 (12.8)
Depot antipsychotics	4 (1.8)	9 (4.1)
Stimulants	4 (1.8)	0

Abbreviation: ITT = intent-to-treat.

eTable 2. Dose and Exposure of Paliperidone Palmitate and Oral Antipsychotics

	Paliperidone Palmitate	Oral Antipsychotics						
		Aripiprazole	Haloperidol	Olanzapine	Paliperidone	Perphenazine	Quetiapine	Risperidone
Dose per injection records, mg, mean (SD)	n = 226 181.3 (34.2)	NA	NA	NA	NA	NA	NA	NA
Dose per prescription records, mg, mean (SD)	NA	n = 33 15.3 (5.9)	n = 15 8.2 (5.3)	n = 36 13.3 (6.4)	n = 48 6.6 (2.4)	n = 20 16.5 (8.8)	n = 29 339.9 (180.4)	n = 37 3.6 (1.6)
Dose per refill records, mg, mean (SD)	NA	n = 25 16.6 (6.6)	n = 11 7.7 (5.4)	n = 31 13.2 (6.5)	n = 43 6.4 (2.5)	n = 18 14.4 (7.5)	n = 24 335.9 (177.4)	n = 30 3.4 (1.5)
Duration of exposure (days)[a]	n = 226	n = 33	n = 15	n = 36	n = 48	n = 20	n = 29	n = 37
Mean (SD)	266.2 (174.5)	239.1 (176.7)	173.5 (160.8)	281.3 (183.6)	272.8 (185.3)	266.8 (168.8)	280.8 (167.8)	324.2 (178.1)
Median (range)	251.5 (30-479)	242.0 (9-492)	137.0 (11-474)	325.0 (22-496)	315.5 (11-506)	270.0 (31-496)	304.0 (8-511)	427.0 (12-491)
Duration category, n (%)								
≤30	18 (8.0)	2 (6.1)	4 (26.7)	4 (11.1)	4 (8.3)	0 (0)	1 (3.4)	1 (2.7)
31-90	37 (16.4)	9 (27.3)	2 (13.3)	5 (13.9)	9 (18.8)	5 (25.0)	3 (10.3)	8 (21.6)
91-180	36 (15.9)	4 (12.1)	2 (13.3)	4 (11.1)	6 (12.5)	1 (5.0)	7 (24.1)	1 (2.7)
181-270	26 (11.5)	2 (6.1)	2 (13.3)	4 (11.1)	4 (8.3)	5 (25.0)	2 (6.9)	3 (8.1)
271-360	9 (4.0)	5 (15.2)	3 (20.0)	1 (2.8)	3 (6.3)	2 (10.0)	4 (13.8)	2 (5.4)
361-450	41 (18.1)	4 (12.1)	1 (6.7)	5 (13.9)	7 (14.6)	3 (15.0)	4 (13.8)	6 (16.2)
>450	59 (26.1)	7 (21,2)	1 (6.7)	13 (36.1)	15 (31.3)	4 (20.0)	8 (27.6)	16 (43.2)

[a]Based on number of injections for the paliperidone palmitate group and number of prescriptions for the oral antipsychotic groups.

eTable 3. Treatment-Emergent Adverse Events (TEAEs) Leading to Study Drug Discontinuation[a,b]

TEAE-Related Study Discontinuation, No. (%)	Paliperidone Palmitate (n = 226)	Oral Antipsychotics (n = 218)
Any	27 (11.9)	17 (7.8)
Body system/Preferred term[c]		
Psychiatric disorders	9 (4.0)	10 (4.6)
Depressive symptom	2 (0.9)	0
Psychotic disorder	2 (0.9)	0
Schizophrenia	1 (0.4)	5 (2.3)
Anxiety	1 (0.4)	2 (0.9)
Insomnia	1 (0.4)	0
Agitation	1 (0.4	0
Abnormal dreams	1 (0.4)	0
Libido decreased	1 (0.4)	0
Substance abuse	1 (0.4)	0
Suicidal ideation	1 (0.4)	0
Paranoid schizophrenia	1 (0.4)	0
Depression	0	2 (0.9)
Auditory hallucination	0	2 (0.9)
Disorganized schizophrenia	0	1 (0.5)
Suicide attempt	0	1 (0.5)
Nervous system disorders	8 (3.5)	8 (3.7)
Akathisia	2 (0.9)	2 (0.9)
Headache	2 (0.9)	0
Dystonia	1 (0.4)	3 (1.4)
Dizziness	1 (0.4)	1 (0.5)
Tardive dyskinesia	1 (0.4)	1 (0.5)
Dyskinesia	1 (0.4)	0
Oromandibular dystonia	1 (0.4)	1 (0.5)
Extrapyramidal disorder	1 (0.4)	0
Parkinsonism	0	2 (0.9)
Reproductive system and breast disorders	6 (2.7)	0
Erectile dysfunction	2 (0.9)	0
Amenorrhea	1 (0.4)	0
Ejaculation failure	1 (0.4)	0
Galactorrhea	1 (0.4)	0
Gynecomastia	1 (0.4)	0
General disorders and administration site conditions	4 (1.8)	0
Injection site pain	2 (0.9)	0
Chest discomfort	1 (0.4)	0
Sudden death	1 (0.4)	0
Investigations	3 (1.3)	0
Weight increased	2 (0.9)	0
Semen volume decreased	1 (0.4)	0

[a]This table comprised data from randomization until the end of randomly assigned treatment (28 days after the last injection of paliperidone palmitate or 1 day after the last dose of oral antipsychotic).
[b]Defined as adverse events with an incidence of ≥1 by body group in either treatment group.
[c]Preferred terms of adverse events were based on version 12.0 of the Medical Dictionary for Regulatory Activities (MedDRA; Medical Dictionary for Regulatory Activities (MedDRA). Version 12.0. http://www.meddra.org. Accessed March 13, 2015).

eTable 4. Treatment-Emergent Prolactin-Related Adverse Events by Preferred Term[a] for Male and Female Subjects[b]

	Paliperidone Palmitate	Oral Antipsychotics
Male subjects, no. (%)	(n = 193)	(n = 190)
Any	42 (21.8)	7 (3.7)
Erectile dysfunction	17 (8.8)	0
Decreased libido	13 (6.7)	3 (1.6)
Increased blood prolactin	7 (3.6)	1 (0.5)
Breast tenderness	2 (1.0)	1 (0.5)
Gynecomastia	3 (1.6)	0
Breast pain	1 (0.5)	0
Sexual dysfunction	1 (0.5)	0
Hyperprolactinemia	4 (2.1)	2 (1.1)
Anorgasmia	3 (1.6)	0
Loss of libido	1 (0.5)	0
Females, no. (%)	(n = 33)	(n = 28)
Any	11 (33.3)	2 (7.1)
Amenorrhea	5 (15.2)	1 (3.6)
Galactorrhea	5 (15.2)	0
Irregular menstruation	2 (6.1)	1 (3.6)
Hyperprolactinemia	2 (6.1)	1 (3.6)
Increased blood prolactin	2 (6.1)	0

[a]Preferred terms of adverse events were based on version 12.0 of the Medical Dictionary for Regulatory Activities (MedDRA; Medical Dictionary for Regulatory Activities [MedDRA]. Version 12.0. http://www.meddra.org. Accessed March 13, 2015).
[b]This table comprised data from randomization until the end of randomly assigned treatment (28 days after the last injection of paliperidone palmitate or 1 day after the last dose of oral antipsychotic).