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A randomized, 13-week study assessing the efficacy and metabolic effects of paliperidone palmitate injection and olanzapine in first-episode schizophrenia patients☆

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ABSTRACT

Background: This study was conducted to evaluate the efficacy and metabolic effects of paliperidone palmitate (PP) injections against oral olanzapine in first-episode schizophrenia (FES) patients.
Methods: Eligible patients were randomized to receive PP or olanzapine. Efficacy assessments and weight-related parameters were assessed at baseline, weeks 1, 5, 9, and endpoint or at early withdrawal. Lipid, glucose, insulin and prolactin were evaluated at baseline and endpoint or at early withdrawal.
Results: The Positive And Negative Syndrome Scale (PANSS) scores declined significantly after treatment in both groups. Significant increases in weight-related parameters from baseline to endpoint were shown in both groups. Although there was no significant difference in PANSS scores and weight-related parameters between the two groups through the whole 13-week study. The increased level of triglyceride and HOMA-IR at endpoint from baseline in the olanzapine group was higher than the PP group. There was a stronger elevation of prolactin level in the PP group.
Conclusions: In summary, PP and olanzapine showed similar improvement in the treatment of FES patients. This study also reinforced the necessity for regular monitoring of metabolic parameters in schizophrenia patients prescribed atypical antipsychotics.
Clinical trial registration numbers: ChiCTR-IOR-14005304.
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1. Introduction

Considered among the most disabling medical disorders, the World Health Organization ranked schizophrenia as one of the top ten illnesses contributing to global disease burden with a life-time prevalence of 0.30–0.66%, increasing to 2.3% in the presence of other psychotic disorders (Perala et al., 2007). As a psychiatric disorder with chronic and recurrent patterns, it requires continuous long-term antipsychotic treatment to manage symptoms, prevent relapse, provide maximum cognitive function, and improve quality of life (Keith et al., 2004; Kramer et al., 2007). However, treatment adherence is particularly challenging in schizophrenia due to various patient-related associations including drug class, social support, concurrent substance abuse, and the effect of symptom domains on adherence, including positive and negative symptoms, lack of insight, depression, and cognitive impairment (Shuler, 2014). Adherence to oral antipsychotic treatment has been shown to be poor (Lieberman et al., 2003), related to clinical and functional deterioration, and increased risk in both relapse and re-hospitalization (Lindenmayer et al., 2009; Nasrallah, 2007; Novick et al., 2010).

The recent development of long acting injectable (LAI) formulations have decreased the incidence of some problems with non-adherence by reducing the need for daily dosing and subsequent fluctuations in plasma concentration, thereby reducing the occurrence of relapse

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(Wehring et al., 2011). Additionally, the healthcare provider can ensure a patient has received the medication treatment (Weiden et al., 2009). LAI formulations have also been reported as highly acceptable to doctors and patients due to rapid identification of non-adherence, convenience, and low relapse frequency (Hough et al., 2010; Schooler, 2003).

Paliperidone palmitate (PP), a LAI antipsychotic, is an approved treatment for acute and maintenance regimens in adult schizophrenia patients in the US (Sustenna®, 2010), European Union, and several other countries including the People's Republic of China and Korea. Recent studies have clarified the efficacy and safety of PP by several methods, including comparison with other LAIs (Li et al., 2011a; McEvoy et al., 2014), dose variation (Pandina et al., 2011), and delay in time-of-relapse (Hough et al., 2010). Most PP studies examined populations where there was a diagnosis of schizophrenia for a course longer than one year. Some studies did not note distinguishable classification in terms of the course of schizophrenia (McEvoy et al., 2014). None of the studies included data on first-episode schizophrenia (FES) patients. Studies based on FES patients have offered the unique opportunity to examine antipsychotic therapeutic treatment and adverse effects in more representative patients where important initial treatment effects take place with less interference from uncontrollable factors. In the study of oral second generation antipsychotics (SGAs), when compared to multiple-episode patients, FES patients have generally shown higher response rates (Robinson et al., 1999), required lower antipsychotic doses, and were more sensitive to adverse effects (Robinson et al., 2005). Since the pharmacokinetics between oral antipsychotics and long acting injections are different, studying long acting injections on FES patients is important in determining the effect among this population.

In recent years, metabolic syndrome (MetS) in patients with schizophrenia has aroused great attention. A meta-analysis revealed that the overall prevalence rate of MetS in individuals with schizophrenia was 32.5% (Mitchell et al., 2013b). The MetS, including visceral adiposity, insulin resistance, increased blood pressure, elevated triglyceride levels, and low high-density lipoprotein (HDL) cholesterol levels, is an important risk factor for cardiovascular disease (Eckel et al., 2005). In addition, antipsychotic drugs especially of second generation contribute to incident risk of MetS (Mitchell et al., 2013b). Metabolic treatment-emergent adverse events, including weight gain and elevated blood levels of glucose, lipids, and insulin, have been reported in patients with schizophrenia during long-term treatment with PP (Sliwa et al., 2014). As MetS has great influence upon future morbidity and mortality, it is very necessary to monitor the changes of metabolic parameters associated with antipsychotic treatment.

Among the various second generation antipsychotics, olanzapine has the well- recognized reliable efficacy in the treatment of schizophrenia, as a previous horizontal study showed that olanzapine was more effective than other SGAs expect amisulpride or clozapine administered (Komossa et al., 2010a). The efficacy of olanzapine in Chinese populations was also confirmed by multiple comparative and noncomparative studies as shown by a systematic literature review (Xue et al., 2014). Therefore, we chose olanzapine as the reference group to measure the effect of PP injection. Our randomized, head-to-head, active-controlled, 13-week study primarily evaluated the efficacy and metabolic effects of PP intramuscular injections with oral olanzapine in Han Chinese first-episode schizophrenia patients.

2. Methods

2.1. Patients

Patients from the First Affiliated Hospital of the Medical School of Zhejiang University that fulfilled the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The Structured Clinical Interview for DSM Disorders (SCID), routine laboratory tests, and physical and neurological examinations were administered to each participant.

The inclusion criteria used in this study for patient selection were: (1) aged between 13 and 45 years old; (2) a DSM-IV diagnosis of schizophrenia with a Positive and Negative Syndrome Scale (PANSS) total score between 60 and 120 at screening; (3) having onset of a first psychotic episode within 24 months of program entry (McCleery et al., 2014); (4) being antipsychotic drug naive; (5) either gender; (6) Han origin; (7) body mass index $\geq 18.0\ kg/m^2$ and $< 30\ kg/m^2$.

The key exclusion criteria were: (1) a primary active DSM-IV-TR I diagnosis other than schizophrenia at screening or a DSM-IV-TR diagnosis of active substance dependence within 3 months prior to screening (except for nicotine or caffeine); (2) a 25% decrease in the PANSS total score between screening and baseline; (3) history of exposure to a psychoactive drug (mood stabilizer, including lithium, any anticonvulsant or illicit mood-altering substances) within 3 months prior to screening; (4) pregnancy, breast feeding or any on-going family planning; (5) history or presence of any unstable systemic disease. During the study, use of other antipsychotics, mood stabilizers, over-the-counter prescriptions or herbal agents with psychoactive properties were not permitted.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Medical School of Zhejiang University. All subjects provided written informed consent before entering into the study. The trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements.

2.2. Study design, medications, randomization and blinding

The study consisted of an initial 2-day screening and oral tolerability testing phase, followed by a randomized, 13-week and active-controlled treatment of first-episode schizophrenia patients in China (ChiCTR-IOR-14005304). Criteria the same, but was adjusted according to the clinical practice.

All eligible patients received oral tolerability testing (3 mg paliperidone extended-release tablets for the first 2 days). Patients were then randomly assigned to either of two groups: PP or olanzapine group based on a computer-generated randomization scheme stratified by the center.

Doses of PP expressed as milligram equivalent (mg eq.) and milligram, with 100 mg eq. equating to 156 mg, were provided as 117, 156 and 234 mg injectable suspensions. Patients in the PP group received PP administration on day 1 (234 mg, deltoid) and day 8 (156 mg, deltoid), followed every 4 weeks by deltoid or gluteal injections according to subject choice on days 36 (78 or 156 mg) and 64 (78, 156, or 234 mg). The investigator could increase or decrease the dose of the study medication on days 36 and 64 depending on assessment of tolerability and efficacy.

Oral olanzapine was supplied as 5 mg tablets. The dose in this group was fixed at 5 mg per day during the 1st week, and could be increased or decreased by the investigator according to assessed tolerability and efficacy after the 1st week. We checked the empty medical boxes at each visit to assess the adherence.

The efficacy and safety assessments were performed by trained practitioners who were blind to the treatment that the patient was receiving. Tolerability was assessed by the medical practitioner during meeting with each patient.

2.3. Concomitant medication

Patients receiving anti-parkinsonian treatment of extrapyramidal symptoms (EPS) and oral benzodiazepines were permitted on to the study; however, benzodiazepine administration was not to be within 6 h prior to scheduled efficacy or safety rating. Anti-parkinsonian medication could be introduced by the investigator if extrapyramidal

symptoms emerged during the study using trihexyphenidyl. Mood stabilizers (including lithium and any anticonvulsants) and any prescription, illicit mood-altering substances, or over-the-counter agents with psychotropic actions were not permitted.

2.4. Assessments

2.4.1. Primary outcome: efficacy assessments

The primary efficacy variable was change in the PANSS total score from baseline to the endpoint (week 13). Secondary efficacy variables included changes from baseline to endpoint in score of PANSS P (positive scale), PANSS N (negative scale), PANSS G (general psychopathology scale) and responder rate (percentage of patients with a 30% or more reduction in PANSS total score). Trained raters with relevant clinical expertise performed all efficacy assessments. They achieved high reliability with each other (Kappa = 0.85) before evaluating subjects. Where possible, the same rater administered the scale at all predetermined visits from baseline to final assessment (weeks 1, 5, and 9, and end of the study or at early withdrawal).

2.4.2. Secondary outcome: metabolic assessments

Metabolic assessments of weight, body mass index (BMI), waist circumference, hip circumference, waist/hip ratio, and subcutaneous fat were measured at baseline, during weeks 1, 5, 9, and at the endpoint or early withdrawal. BMI was computed as body weight (kg) divided by the square of height (m^2). Waist circumference was measured at the horizontal plane of umbilicus, and hip circumference at the level of the maximum posterior extension of the buttocks. The waist/hip ratio was used as a measure of upper body adiposity. Subcutaneous fat was assessed using skin fold measurements. The skin fold was measured at the diagonal midway between umbilicus and right anterior superior iliac spine (Himes et al., 1979). All measurements were repeated 3 times for each patient, and the mean of the 3 values was reported.

Patient fasting metabolic assessments were taken at baseline and endpoint for fasting high density lipoprotein (HDL), low density lipoprotein (LDL), fasting cholesterol, fasting triglycerides, fasting serum glucose, insulin, haemoglobin A1c (HbA1c)%, homeostasis β-cell function (HOMA-β), homeostasis model of assessment for insulin resistance index (HOMA-IR) (Rudenski et al., 1991) and prolactin. HOMA-β was calculated as (20 × FPI)/(FPG − 3.5) (Matthews et al., 1985), whereas HOMA-IR = (FPI × FPG)/22.5, in which FPI was the fasting plasma insulin concentration (mU/l) and FPG was fasting plasma glucose (mmol/l).

All laboratory analyses were performed at the central biochemical laboratory of the First Affiliated Hospital, College of Medicine, Zhejiang University. Fasting serum glucose, LDL, HDL, cholesterol and triglycerides were measured by colorimetric (Hitachi Model 7600 Series Automatic Analyzer). Insulin and prolactin were assayed using a Chemiluminesent Microparticle ImmunoAssay (CMIA). HbA1c was assayed using ion-exchange chromatography (Bio-Rad Glycohemoglobin Analyzer).

2.4.3. Safety assessments

Safety assessments including vital signs, physical and neurological examination, were conducted daily in hospital, at week 1 and subsequent 4-weekly intervals post-discharge. ECG was performed every 4 weeks. Treatment-emergent adverse events (TEAEs) were evaluated and recorded from baseline to final assessment (weeks 1, 5, and 9, and end of the study or at early withdrawal). The Drug-Induced Extrapyramidal Symptoms Scale 14 was used to evaluate the severity of drug induced extrapyramidal symptoms. Injection site pain examinations were performed by a Visual Analog Scale (0 [no pain] to 100 [maximum pain level]) as well as injection site reactions.

2.5. Statistical analysis

The intent to-treat (ITT) analysis set included all randomized patients who received at least one dose of study drug, and had one PANSS total score assessment at baseline at least one after baseline. The per-protocol analysis set included all randomized patients who completed the study without major protocol deviations. Efficacy variables were primarily analyzed in the ITT set, including PANSS total score and subscales using the last observation carried forward (LOCF) method. In order to provide better reference, responder rate was analyzed in both ITT and per protocol analysis set. The weight related metabolic effects analysis set included all patients who received at least one dose of study drug and had a weight related measure at baseline and at least one after baseline. The lipid, glucose-insulin and prolactin analysis set comprised all randomized patients who received at least one dose of study drug and had a blood metabolic measurement at baseline and at least one after. The safety analysis set included all patients who received at least one dose of study medication.

The continuous variables are described using mean ± standard deviation (SD). We adopt the mixed effect model for the repeated measured data. The mixed procedure was used to do a global assessment of the effect of treatment groups (GROUP), time of therapy (TIME) and the interaction between GROUP and TIME. The contrast statement was used to do a comparison of the average level of each variable between GROUP/TIME after controlling the influence of TIME/GROUP. The *P* value is two-sided. A Cochran-Mantel-Haenszel test was used to analyze the percentages of PANSS responders. The lipid, glucose, insulin and prolactin effects within group were assessed by paired sample t-test, and the differences of mean change from baseline to endpoint through treatment between two groups used independent sample t-test. Safety results were assessed using descriptive statistics and chi-squared test in the safety analysis set. The significance level was 5%. All statistical tests were using SAS software (Version 9.2; SAS Institute, Cary, NC, USA).

3. Results

3.1. Subject disposition, baseline demographics, and clinical characteristics

The patients were recruited from December 5, 2014 to December 16, 2015, the follow-up visits were complete before March 20, 2016. A total of 66 patients were enrolled, with 9 patients failing at screening. Resulting 57 patients completed 2-day screening and oral tolerability test and were randomized to receive either PP or olanzapine. A final 51 (89.5%) patients completed the study, with 6 (10.5%) being withdrawn (Fig. 1). The ITT analysis set included 28 patients in the PP group and 29 in the olanzapine group, and these populations used in the efficacy and weight related measurement analysis. For the per-protocol analysis set, 26 and 25 patients completed the study in the PP and olanzapine groups, respectively. Similarly, these populations had a baseline and at least one post-baseline blood metabolic measurement used in lipid, glucose-insulin and prolactin effects analysis. The safety analysis includes all 57 patients that underwent randomization.

Demographic and baseline characteristics were comparable across treatment groups (Table 1). Patients' ages ranged from 14 to 42 years with a mean (SD) of 21.54 (± 5.60) in PP and 23.79 (± 5.89) in olanzapine group. 67.8% of schizophrenic patients in the PP group and 68.9% in the olanzapine group were diagnosed paranoid type.

3.2. Primary outcome: treatment effect

The mean (SD) dose for PP was 128.85 (± 28.01) mg eq. at endpoint. Olanzapine group received 17.80 (± 3.56) mg at endpoint.

The main effect of time (PP: $F = 48.92$, $p < 0.001$; olanzapine: $F = 73.66$, $p < 0.001$) showed that the Positive And Negative Syndrome Scale (PANSS) total score and subscale scores declined

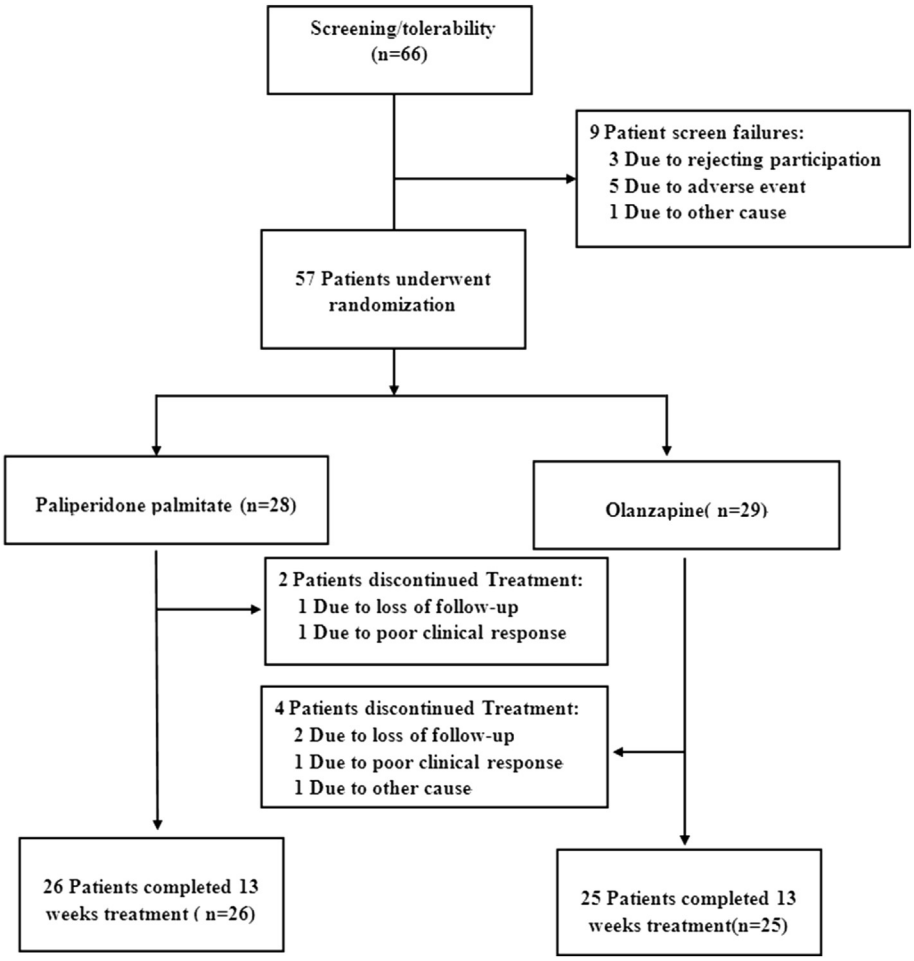

Fig. 1. Consort flow chart.

Table 1
Comparison of baseline characteristics of patients randomly assigned to paliperidone palmitate and olanzapine.

Measure	Paliperidone palmitate (n = 28)	Olanzapine (n = 29)	t/χ^2	p
Age, mean ± SD (year)	21.54 ± 5.60	23.79 ± 5.89	1.482[a]	0.144
Sex (male/female)	17/11	20/9	0.514[b]	0.426
Nationality:Han/other (n)	28/0	29/0		
Occupation			1.197[b]	0.550
Student	10	12		
Employed	15	16		
Unemployed	3	1		
DSM-IV subtype			0.408[b]	0.815
Paranoid type	19	20		
Disorganized type	1	2		
Undifferentiated type	8	7		
Course of illness (months)	12.64 ± 11.12	7.90 ± 8.65	−1.422[a]	0.163
Family history (n)	2	2	0.001[b]	0.971

[a] t-test.
[b] χ^2 test.

significantly after treatment in both groups using repeated-measures ANOVA. The time × group interaction was significant in the PANSS N score (F = 9.46, p = 0.008). Although there was no significant difference between the two groups through the whole 13-week study (all p > 0.01).

The mean (SD) decrease of the PANSS total score at endpoint verses baseline was 32.71 (± 19.49), d = 1.68 in the PP group and 36.62 (± 17.09), d = 1.99 in the olanzapine group. While there was no significant difference between the two groups (all P > 0.01).

In the ITT analysis set, the percentage of patients who had a PANSS total score decrease over 30% at endpoint verses baseline was 67.9% in the PP group and 75.8% in the olanzapine group, although no significance was observed. In the per-protocol analysis set for PP and olanzapine groups, the percentage was 73.1% and 88%, respectively, also with no statistical difference. See Table 2 for summary of statistical analyses.

In general, the two groups did not differ significantly in the change of PANSS total scores across the 13-week trial. See Table 2 for summary of statistical analyses.

3.3. Secondary outcome: metabolic assessments

Data of weight-related metabolic effects over the 13-week trail are listed in Table 3. In terms of weight change, the interaction effect between time and group was not significant (F = 0.76, p = 0.553), and the overall within-group effect showed a significant increase in both PP and olanzapine groups (F = 18.43, p < 0.001; F = 25.15, p < 0.001, respectively). The mean (SD) weight gain in the PP group (3.64 [± 4.98] kg) was less than in the olanzapine group (4.86 [± 3.26] kg), although there was no significant difference between the two groups through the whole 13-week study.

Interaction effect of BMI showed no significance, and we found that the BMI increase in both groups was significant (F = 18.96, p < 0.001; F = 21.60, p < 0.001, respectively), whereas no difference was observed between the PP and olanzapine groups in BMI (F = 0.00, p = 0.947).

Similarly, both waist and hip circumferences increased across time in both groups, whereas no difference was observed between PP and

Table 2
The treatment effect in two treatment groups.

PANSS score	Paliperidone palmitate (n = 28)	Olanzapine (n = 29)	F[a]	p	Conhen's d	F[b]	F[c]	Time	Group	[d]Time × group
Total scores										
Baseline	87.39 ± 20.46	88.44 ± 13.55	0.08	0.778	0.06	F = 48.92	F = 73.66	F = 119.58	F = 0.03	F = 2.57
1 week	72.32 ± 12.18	79.72 ± 12.18	3.92	0.049	0.61	p < 0.001	p < 0.001	p < 0.001	p = 0.872	p = 0.039
5 weeks	64.75 ± 16.12	64.03 ± 12.40	0.04	0.848	0.05					
9 weeks	58.21 ± 12.07	55.69 ± 13.79	0.46	0.500	0.20					
13 weeks	54.68 ± 10.07	51.82 ± 12.30	0.58	0.446	0.26					
P scores										
Baseline	22.07 ± 6.81	19.93 ± 4.72	2.91	0.089	0.37	F = 51.05	F = 39.16	F = 89.02	F = 0.35	F = 13.9
1 week	17.39 ± 5.317	17.55 ± 4.31	0.02	0.899	0.03	p < 0.001	p < 0.001	p < 0.001	p = 0.556	p = 0.237
5 weeks	14.96 ± 5.52	14.55 ± 4.60	− 0.11	0.743	0.08					
9 weeks	12.64 ± 4.53	12.76 ± 3.71	0.01	0.926	0.03					
13 weeks	12.18 ± 3.99	11.41 ± 2.80	0.37	0.542	0.23					
N scores										
Baseline	19.78 ± 6.11	21.93 ± 7.27	2.29	0.132	0.32	F = 16.99	F = 70.69	F = 77.29	F = 0.06	F = 9.46
1 week	17.53 ± 5.86	20.14 ± 6.41	3.37	0.068	0.43	p < 0.001	p < 0.001	p < 0.001	p = 0.800	p = 0.008
5 weeks	15.61 ± 4.89	15.00 ± 4.91	0.18	0.669	0.13					
9 weeks	14.50 ± 4.93	11.83 ± 4.65	3.56	0.061	0.56					
13 weeks	13.53 ± 3.13	10.55 ± 4.04	4.43	0.036	0.83					
G scores										
Baseline	40.07 ± 9.42	40.65 ± 6.28	0.10	0.755	0.07	F = 39.59	F = 46.10	F = 84.41	F = 0.65	F = 1.17
1 week	33.25 ± 7.47	36.83 ± 5.25	3.67	0.057	0.56	p < 0.001	p < 0.001	p < 0.001	p = 0.421	p = 0.327
5 weeks	30.25 ± 8.49	30.76 ± 6.71	0.07	0.786	0.07					
9 weeks	27.53 ± 6.63	27.76 ± 7.22	0.01	0.905	0.03					
13 weeks	25.53 ± 5.48	26.62 ± 6.55	0.34	0.562	0.18					

The mean (SD) decrease of the PANSS total score, P score, N score and G score at endpoint verses baseline was 32.71 (± 19.49), d = 1.68, 9.89 (± 5.65), d = 1.75, 6.25 (± 5.18), d = 1.21, 14.54 (± 9.13), d = 1.59 respectively in the PP group and 36.62 (± 17.09), d = 1.99, 8.52 (± 5.90), d = 1.45, 11.38 (± 6.56), d = 1.73, 14.03 (± 8.98), d = 1.56 respectively in the olanzapine group.

[a] The differences between paliperidone palmitate and olanzapine group at all point times, threshold of $P < 0.01$.

[b] The overall effects of paliperdone palmitate.

[c] The overall effects of olanzapine.

[d] The PANSS score of paliperidone versus olanzapine over time, drug × time interaction.

olanzapine groups. However, waist/hip ratio didn't change significantly from baseline in either group, and no difference between the two groups was observed.

Subcutaneous fat was demonstrated to increase in both PP and olanzapine groups (F = 19.31, p < 0.001; F = 7.91, p < 0.001, respectively), with no significance (F = 0.14, p = 0.706) between the two groups being observed. See Table 3 for summary of statistical analyses.

Lipid, glucose, insulin and prolactin effects were based on patients who completed the study (PP, n = 26; olanzapine, n = 25) (Table 4).

Fasting triglyceride and HOMA-IR increased only in the olanzapine group (t = 3.617, p = 0.001, d = 0.72; t = 3.114, p = 0.004, d = 0.62 respectively), but not in the PP group (t = 0.096, p = 0.924, d = 0.02; t = 1.788, p = 0.085, d = 0.35 respectively). The increased level of triglyceride and HOMA-IR at endpoint from baseline in the olanzapine group was higher than the PP group (t = − 2.893, p = 0.005, d = 0.77; t = − 2.122, p = 0.038, d = 0.58 respectively).

Fasting LDL, cholesterol, glucose and insulin levels increased only in the olanzapine group (t = 2.090, p = 0.046, d = 0.42; t = 2.759, p = 0.010, d = 0.55; t = 2.487, p = 0.019, d = 0.50; t = 2.940, p = 0.007, d = 0.59 respectively), but no difference were observed between the two groups.

Fasting HDL, HbA1c and HOMA-β didn't change significantly from baseline in either group, and no differences between groups was observed.

Prolactin level increased in both PP and olanzapine groups (t = 3.366, p = 0.002, d = 0.66; t = 4.068, p < 0.001, d = 0.81 respectively), with a stronger elevation in the PP group through treatment (t = 2.300, p = 0.025, d = 1.08). See Table 4 for summary of statistical analyses.

3.4. Safety findings

Treatment-emergent adverse events (TEAEs) listed in Table 5. Discontinuations due to TEAEs occurred in 2 (of 7) in the PP group and 1 (of 8) in the olanzapine group. One patient developed acute dystonia and the other one could not endure the weight gain and menstrual disturbance in the PP group. Discontinuation in the olanzapine group was caused by intolerant dizziness. Somnolence was the most common psychiatric TEAE; 6 patients (21.5%) in the PP group and 17 (58.5%) in the olanzapine group reported suffering from this problem. Common EPS-related events include akathisia (PP: n = 7 [25%], olanzapine: n = 2 [7%]) and tremor (PP: n = 6 [21.5%], olanzapine: n = 2 [7%]). Gastrointestinal symptoms were common in both groups, including dry mouth and constipation.

No serious cardiac-related adverse event was reported during the study, and no patient showed clinically noteworthy changes in QTc interval from baseline to endpoint. Tachycardia (defined as heart rate over 100 bpm) occurred in 7 patients [25%] in the PP group and 8 patients [27.5%] in the olanzapine group. Two patients in the PP, and 1 in the olanzapine, group reported orthostatic hypotension (defined as a decrease in systolic [> 20 mmHg] or diastolic [> 10 mmHg] blood pressure after standing for at least 2 min and an increase in pulse rate > 15 bpm compared to supine position).

Prolactin-related adverse events were observed in 4 patients (14%) in the PP, and 1 patient (3.5%) in the olanzapine, group.

In the PP group, injection site pain and swelling were reported by 14 patients (50%) and 5 patients (18%), respectively, but tolerated by all participants. Injection site pain was evaluated in the PP group, but not applicable to the olanzapine group.

There were no clinically relevant changes in vital signs, clinical or hematological laboratory test results during the study. No reports were made of ventricular tachycardia, ventricular fibrillation, torsade de pointes, hyperthermia, anaphylactic reaction, pancreatitis-related

Table 3
Weight-related metabolic effects of paliperidone palmitate and olanzapine during 13 weeks of treatment.

Metabolic and other measures	Paliperidone palmitate (n = 28)	Olanzapine (n = 29)	F[a]	p	Conhen's d	F[b]	F[c]	Time	Group	[d]Time × group
Weight (kg)										
Baseline	56.95 ± 9.93	57.99 ± 11.28	0.12	0.726	0.10	F = 18.43	F = 25.15	F = 42.70	F = 0.31	F = 0.76
1 week	57.16 ± 10.07	59.04 ± 11.42	0.42	0.517	0.18	p < 0.001	*p* < 0.001	p < 0.001	*p* = 0.581	P = 0.553
5 weeks	58.64 ± 10.33	60.11 ± 11.16	0.26	0.613	0.14					
9 weeks	60.22 ± 10.38	61.52 ± 11.74	0.20	0.653	0.12					
13 weeks	60.59 ± 10.90	62.82 ± 11.90	0.59	0.442	0.20					
BMI										
Baseline	20.42 ± 2.71	20.35 ± 3.07	0.01	0.935	0.02	F = 18.96	F = 21.60	F = 40.19	F = 0.00	F = 0.32
1 week	20.51 ± 2.87	20.68 ± 3.02	0.04	0.841	0.06	p < 0.001	p < 0.001	p < 0.001	p = 0.947	p = 0.863
5 weeks	21.02 ± 2.94	21.06 ± 2.96	0.00	0.962	0.01					
9 weeks	21.60 ± 3.03	21.54 ± 3.10	0.01	0.943	0.02					
13 weeks	21.83 ± 3.26	22.01 ± 3.22	0.05	0.823	0.06					
Waist circumferences (cm)										
Baseline	76.28 ± 8.25	75.71 ± 8.40	0.07	0.797	0.07	F = 18.69	F = 19.85	F = 38.43	F = 0.03	F = 0.09
1 week	76.81 ± 8.42	76.51 ± 8.18	0.02	0.894	0.04	p = 0.003	p < 0.001	p < 0.001	p = 0.870	p = 0.986
5 weeks	77.88 ± 8.55	77.77 ± 8.03	0.00	0.961	0.01					
9 weeks	79.52 ± 8.85	79.12 ± 8.25	0.03	0.857	0.05					
13 weeks	80.46 ± 9.00	80.07 ± 8.31	0.03	0.858	0.05					
Hip circumferences (cm)										
Baseline	90.49 ± 6.22	90.10 ± 8.16	0.04	0.844	0.05	F = 4.13	F = 11.36	F = 14.23	F = 0.28	F = 1.14
1 week	90.39 ± 6.06	90.67 ± 7.78	0.02	0.885	0.04	p = 0.0030	p < 0.001	p < 0.001	p = 0.600	p = 0.341
5 weeks	91.08 ± 8.07	92.63 ± 7.75	0.63	0.429	0.20					
9 weeks	92.95 ± 6.47	94.13 ± 7.81	0.37	0.545	0.17					
13 weeks	93.10 ± 7.02	95.14 ± 7.98	1.08	0.301	0.27					
Waist/hip ratio										
Baseline	0.84 ± 0.08	0.84 ± 0.05	0.04	0.850	0.00	F = 1.59	F = 0.09	F = 1.06	F = 0.44	F = 0.63
1 week	0.85 ± 0.08	0.84 ± 0.06	0.11	0.743	0.14	p = 0.1788	p = 0.9868	p = 0.3752	p = 0.506	p = 0.638
5 weeks	0.85 ± 0.07	0.84 ± 0.07	0.66	0.417	0.14					
9 weeks	0.85 ± 0.07	0.84 ± 0.07	0.44	0.508	0.14					
13 weeks	0.86 ± 0.07	0.84 ± 0.08	1.13	0.289	0.27					
Subcutaneous fat (mm)										
Baseline	23.46 ± 6.89	23.31 ± 6.85	0.01	0.942	0.02	F = 19.31	F = 7.91	F = 25.94	F = 0.14	F = 1.48
1 week	23.73 ± 6.91	24.04 ± 7.14	0.02	0.877	0.04	p < 0.001	p < 0.001	p < 0.001	p = 0.706	p = 0.208
5 weeks	25.22 ± 7.20	24.89 ± 7.38	0.03	0.872	0.05					
9 weeks	27.16 ± 7.56	25.81 ± 7.69	0.45	0.503	0.18					
13 weeks	29.37 ± 9.25	27.32 ± 8.83	1.03	0.311	0.23					

The mean (SD) increase of the weight, BMI, waist circumferences, hip circumferences, waist/hip ratio and subcutaneous fat at endpoint verses baseline was 3.64 (± 4.98), d = 0.73, 1.42 (± 1.92), d = 0.74, 4.18 (± 5.09), d = 0.82, 2.62 (± 7.60), d = 0.34, 0.02 (± 0.06), d = 0.31, 5.91 (± 7.07), d = 0.84 respectively in the PP group and 4.86 (± 3.26), d = 1.49, 1.66 (± 1.16), d = 1.43, 4.36 (± 3.69), d = 1.18, 5.03 (± 6.09), d = 0.83, 0.003(± 0.05), d = 0.06, 4 (± 4.05), d = 0.99 respectively in the olanzapine group.

[a] The differences between paliperidone palmitate and olanzapine group at all point times.

[b] The overall metabolic effects of paliperdone palmitate.

[c] The overall metabolic effects of olanzapine.

[d] The overall metabolic effects of paliperidone palmitate versus olanzapine over time, drug × time interaction.

adverse events, neuroleptic malignant syndrome, potential rhabdomyolysis-related event, or potential syndrome of inappropriate antidiuretic hormone secretion–related events.

4. Discussion

In our study, PP and olanzapine showed similar efficacy in the treatment of first-episode schizophrenia patients at endpoint. Our findings are similar to the results of a 13-week, double-blind study on non-FES demonstrating the non-inferiority of PP versus risperidone LAI (Pandina et al., 2010). It should be emphasized that olanzapine is a well-recognized second generation antipsychotic in the treatment of schizophrenia, as a previous horizontal study showed that olanzapine had greater efficacy compared to other SGAs expect amisulpride or clozapine administered (Komossa et al., 2010b). Furthermore, the present study focused on the FES population and these patients were thought to respond better. In one olanzapine study, the FES patients had a response rate of 67.2%, which was significantly greater compared to the multiple-episode patient's response rate of 45.1% (Sanger et al., 1999). The response rate observed in the current study was 67.9% in the PP group and 75.8% in the olanzapine group, higher than previous studies. While no significance was observed between the two groups. Thus, we speculate that PP also has reliable efficacy in the treatment of FES patients.

The mean (SD) weight gain in the PP group (3.64 [± 4.98] kg) was less than that in the olanzapine group (4.86 [± 3.26] kg), although there was no significant difference between the two groups in our 13-week study. A previous head-to-head meta-analysis of the metabolic side effects of SGAs revealed that olanzapine produced significantly more weight gain than amisulpride, aripiprazole, quetiapine, risperidone or ziprasidone. The extent of olanzapine induced weight gain was 2–3 kg more than risperidone over a time span of 2 to 6 months in an unclassified population (Komossa et al., 2010b). Since paliperidone is the primary active metabolite of the older antipsychotic risperidone, we hypothesized that olanzapine would produce more weight gain, while no difference was observed in our study. As to recent studies concerning PP caused weight gain, Li calculated a mean (SD) increase in bodyweight of 1.1 (± 3.36) kg in the PP group over their 13-week study based on the population with a schizophrenia course > 1 year (Pandina et al., 2011), which was similar to results of another 13-week study of 1.5 (± 3.10) kg (Li et al., 2011b). Both of these figures were less than the result of our study. We attributed this difference to the unmedicated

Table 4
Lipid, glucose-insulin and prolactin effects of paliperidone palmitate and olanzapine during 13 weeks of treatment.

Metabolic and other measures	Paliperidone palmitate (n = 26)	Olanzapine (n = 25)	t[a]	p	Conhen's d	t[b]	t[c]	t[e]
HDL fasting (mmol/l)								
Baseline	1.36 ± 0.28	1.30 ± 0.30	− 0.753	0.455	0.21	t = 1.073	t = 1.073	t = − 0.476
13 weeks	1.70 ± 1.47	1.47 ± 0.81	− 0.698	0.489	0.19	p = 0.293	p = 0.293	p = 0.637
						d = 0.21	d = 0.21	d = 0.13
LDL fasting (mmol/l)								
Baseline	2.10 ± 0.70	2.29 ± 0.46	1.176	0.246	0.32	t = 0.357	t = 2.090	t = − 1.612
13 weeks	2.13 ± 0.51	2.63 ± 0.87	2.591	0.012	0.70	p = 0.724	p = 0.046	p = 0.113
						d = 0.07	d = 0.42	d = 0.43
Cholesterol fasting (mmol/l)								
Baseline	3.93 ± 0.81	4.13 ± 0.73	0.987	0.328	0.26	t = 0.834	t = 2.759	t = − 1.989
13 weeks	4.02 ± 0.83	4.70 ± 1.08	2.656	0.011	0.71	p = 0.411	p = 0.010	p = 0.052
						d = 0.16	d = 0.55	d = 0.53
Triglyceride fasting (mmol/l)								
Baseline	0.88 ± 0.34	0.91 ± 0.74	0.201	0.841	0.05	t = 0.096	t = 3.617	t = − 2.893
13 weeks	0.89 ± 0.49	1.35 ± 0.80	2.645	0.011	0.70	p = 0.924	p = 0.001	p = 0.005
						d = 0.02	d = 0.72	d = 0.77
Glucose fasting (mmol/l)								
Baseline	4.87 ± 0.48	4.89 ± 0.62	0.108	0.914	0.04	t = 0.571	t = 2.487	t = − 1.720
13 weeks	4.92 ± 0.34	5.20 ± 0.61	2.100	0.040	0.57	p = 0.573	p = 0.019	p = 0.091
						d = 0.11	d = 0.50	d = 0.46
Insulin fasting (mIU/l)								
Baseline	9.43 ± 4.12	9.23 ± 3.62	− 1.193	0.848	0.05	t = 1.600	t = 2.940	t = − 1.899
13 weeks	10.51. ± 5.15	13.14 ± 8.26	1.448	0.154	0.38	p = 0.121	p = 0.007	p = 0.065
						d = 0.31	d = 0.59	d = 0.50
HbA1c (%)								
Baseline	6.83 ± 0.47	6.82 ± 1.27	− 0.059	0.953	0.01	t = − 1.110	t = − 0.206	t = − 0.081
13 weeks	6.76 ± 0.46	6.75 ± 0.93	0.041	0.968	0.01	p = 0.277	p = 0.839	p = 0.935
						d = 0.22	d = 0.04	d = 0.02
HOMA-β								
Baseline	165.29 ± 124.5	167.55 ± 114.66	0.071	0.944	0.02	t = − 0.322	t = 0.710	t = − 0.737
13 weeks	160.66 ± 97.73	172.07 ± 110.10	0.415	0.680	0.11	p = 0.750	p = 0.484	p = 0.464
						d = 0.06	d = 0.14	d = 0.10
HOMA-IR								
Baseline	2.04 ± 0.89	1.99 ± 0.77	− 0.215	0.831	0.06	t = 1.788	t = 3.114	t = − 2.122
13 weeks	2.30 ± 1.06	3.10 ± 2.11	1.839	0.073	0.48	p = 0.085	p = 0.004	p = 0.038
						d = 0.35	d = 0.62	d = 0.58
Prolactin, μg/l								
Baseline	26.76 ± 25.86	23.80 ± 14.33	− 0.537	0.593	0.14	t = 3.366	t = 4.068	t = 2.300
13 weeks	58.15 ± 35.66	27.65 ± 18.18	− 4.087	0.000	1.07	P = 0.002	P < 0.001	P = 0.025
						d = 0.66	d = 0.81	d = 1.08

[a] The differences between paliperidone palmitate and olanzapine group at all point times.
[b] The differences between baseline and endpoint in paliperidone palmitate group.
[c] The differences between baseline and endpoint in olanzapine group.
[e] The differences of mean change from baseline to endpoint between paliperidone palmitate and olanzapine group.

feature of our samples, avoiding bias from complicated antipsychotic medication history. Therefore, actual weight gain might exceed estimates for the FES population. The underlying mechanisms of weight gain are not completely understood. Antipsychotic drug is usually the first consideration and feeding behavior is associated with dopamine and serotonin (Dela Cruz et al., 2012; Meguid et al., 2000). Paliperidone demonstrates an affinity that is high for 5-HT_{2A}, but comparatively lower for D_2 receptors, and far less for other 5-HT receptor subtypes (Chue and Chue, 2012). Olanzapine shows significant in vitro inhibitory activity at dopamine D_1, D_2, D_4, 5-HT_{2A}, 5-HT_{2C}, H1, α_1-adrenergic and muscarinic receptor sites, which is greater for 5-HT_2 than for dopamine D_2 receptors (Fulton and Goa, 1997). These mediated neurotransmitter effects may play a major role in the observed weight gain. Furthermore, some behavioral factors, such as physical inactivity or poor cardio-respiratory fitness are also associated with weight gain as well as metabolic syndrome (Koivukangas et al., 2010). The impact on weight requires a study with a larger sample population and longer time to be determined conclusively.

Dyslipidemia was observed in our study. Fasting triglyceride showed a significant increase only in the olanzapine group; significantly more than that in the PP group at endpoint compared to baseline. Fasting LDL and cholesterol level increased only in the olanzapine group, but no difference was observed between the two groups. Previous studies have shown that patients treated with clozapine or olanzapine had higher triglyceride level (Smith et al., 2005) and cholesterol level (Lindenmayer et al., 2003) than risperidone-treated patients. A comparative study in first-episode psychosis patients also confirmed this phenomenon (Zhang et al., 2013a). It's not strange because clozapine and olanzapine upregulate the transcription of sterol regulatory element-binding proteins (SREBP)-1 and/or SREBP-2, which play a key role in hepatic lipid synthesis (Lauressergues et al., 2010), as well as in carbohydrate-induced hypertriglyceridemia (Moon et al., 2012).

Glucose, insulin and HOMA-IR showed a significant increase only in the olanzapine group, not in PP group. HbA1c and HOMA-β showed no increase in both group and no difference between the two groups in our study. Few studies have taken HOMA-IR and HOMA-β into comparison. A recent 12-week comparison of paliperidone extended-release and olanzapine reported similar results: olanzapine produced a significant increase in fasting glucose and a trend toward increasing fasting insulin,

Table 5
Treatment-emergent adverse events reported in schizophrenia patients in two treatment groups.

	Paliperidone palmitate (n = 28) n (%)	Olanzapine (n = 29) n (%)	χ^2	p
Central and peripheral nervous system symptoms				
Dizziness	9(32)	10(34.5)	0.035	0.851
Headache	3(11)	2(7)	0.259	0.610
Tremor	6(21.5)	2(7)	2.493	0.114
Hypertonia	3(11)	1(3.5)	1.153	0.283
Akathisia	7(25)	2(7)	3.511	0.061
Psychiatric symptoms				
Psychotic disorder	3(11)	3(10)	0.002	0.964
Somnolence	6(21.5)	17(58.5)	8.187	0.004*
Insomnia	4(14)	1(3.5)	1.976	0.160
Agitation	6(21.5)	5(17)	0.160	0.689
Anxiety	6(21.5)	5(17)	0.160	0.689
Gastrointestinal system symptoms				
Nausea	6(21.5)	4(14)	0.574	0.449
Vomiting	2(7)	1(3.5)	0.390	0.532
Dry mouth	8(28.5)	7(24)	0.144	0.704
Constipation	10(36)	11(38)	0.030	0.862
Cardiovascular symptoms				
Orthostatic hypotension	2(7)	1(3.5)	0.390	0.532
Tachycardia	7(25)	8(27.5)	0.049	0.825
Others				
Weight increased (> 7%)	11(39)	12(41)	0.026	0.872
Prolactin-related adverse events	4(14)	1(3.5)	2.091	0.148
Injection site pain	14(50)			
Injection site swelling	5(18)			

* $p < 0.05$

with an overall increase of HOMA-IR in both groups (Lin et al., 2013). However, some previous studies have provided confusing results in glucose metabolism.For instance, one meta-analysis showed that glucose changes caused by olanzapine, risperidone, amisulpride, and quetiapine haloperidol group were similar, but with high heterogeneity across studies (Zhang et al., 2013b).

Weight gain, dyslipidemia, glucose disturbance and insulin resistance may lead to the incidence of MetS. Recently, increased prevalence of central obesity and glucose abnormalities suggest metabolic disturbances begin prior to starting medication (Cohen and Hert, 2011). Evidence for this hypothesis is that risk of diabetes is increased in first-degree relatives of patients with schizophrenia (Kohen, 2004). Nonetheless, another study found no difference in metabolic disturbances between un-medicated and medicated first-episode patients (Mitchell et al., 2013a). More research is still required to understand the effect of schizophrenia on metabolic disturbances in the early stage of illness. Previous literature found that olanzapine treatment was characterized by a more deteriorated metabolic risk factor profile compared with risperidone (Almeras et al., 2004) and most other SGAs (Komossa et al., 2010b). Another study found that in patients who develop MetS with at least one year atypical antipsychotic exposure, 42% were receiving olanzapine, 32.8% received risperidone, and 17.2% received paliperidone (Said et al., 2012). Furthermore, the population is also related to MetS prevalence. Generally, multiple episode patients were thought to be more vulnerable to MetS than drug naïve patients. Malhorta reported that the prevalence of MetS was 3–26% in drug naïve patients, while the prevalence reached 69% in medicated patients (Malhotra et al., 2013). The FES population should initially receive low MetS risk treatment or be given effective weight-loss strategies when taking higher risk medication. All patients who start antipsychotic treatment should undergo routine monitoring of weight and metabolic parameters, which is also a direction for further research.

Prolactin elevation occurs in both groups, but more in the PP group. Prolactin elevation can interfere with the function of reproductive, endocrine, and metabolic systems, and in the short-term lead to galactorrhea, gynecomastia, secondary dysregulation effects to hypothalamic-pituitary-gonadal axis, menstrual irregularities, sexual dysfunction, and depression. Long-term elevation can contribute to decreased bone density, osteoporosis and cancer (Byerly et al., 2007). The prolactin level was significantly increased in the PP group compared to the olanzapine group, which was inconsistent with previous studies. It's may be due to an insufficient course of our study as the occurrence of prolactin-related TEAE showed no significance. About 80–90% of serum prolactin is monomeric, with the dimeric form comprising 8–20% and the polymeric 1–5% (Lewis et al., 1989). The larger molecular mass isoforms, termed macroprolactin, the more decreased biological activity and clearance (Hoffmann et al., 1993). Consequently, prolactin level increase may be detected without any clinical prolactin-related TEAE. Another probable explanation for this inconsistency is that the patients in this study were not actively asked whether they had different prolactin-related symptoms at baseline or endpoint. Hyperprolactinemia can also decrease insulin sensitivity (Ben-Jonathan et al., 2006). The relationship between hyperprolactinemia and insulin sensitivity in patients taking antipsychotics needs more study.

We wish to acknowledge several limitations in our study. The relatively small sample size attenuated a more robust conclusion, but this is inevitable due to a relatively small FES population. In addition, the subjects include both adolescent and adult FES patients. We did not divide samples by age into adolescent and adult FES patient groups, again because of the relatively small sample size. This is a single center research, carrying out a multi-center study in the future would increase the sample size and develop results with greater certainty. Because of the different pharmaceutical dosages, this was not a double-blind study. In order to protect the safety of patients, those patients with BMI $\geq 30\ kg/m^2$ were not included in this study. The course of our study was limited to 13 weeks, further research is required to clarify the long-term efficacy and adverse effects of PP in FES population. The prevention of relapse, which is very important, should be evaluated in such longer-term studies. Finally, no structured scale of adverse effects was used in this study, adverse effects should be recorded more detailedly.

In conclusion, PP and olanzapine showed similar improvement in the treatment of FES patients. This study also reinforced the necessity for regular monitoring of metabolic parameters in schizophrenia patients prescribed atypical antipsychotics.

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Ethical statement

The study was approved by the Ethics Committee of the First Affiliated Hospital of Medical School of Zhejiang University. All subjects provided written informed consent before entering into the study. The trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements.

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