Hindawi
Perspectives in Psychiatric Care
Volume 2023, Article ID 3237737, 9 pages
https://doi.org/10.1155/2023/3237737

Research Article

Importance of Long-Acting Injectable Antipsychotic Preparation, Administration, and Injection Site Tolerability: A Focus on Paliperidone Palmitate Once-Every-6-Months Formulation

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Received 5 June 2023; Revised 1 November 2023; Accepted 17 November 2023; Published 19 December 2023

Academic Editor: Francesco Bartoli

Purpose. This post hoc analysis assessed the importance of proper paliperidone palmitate (PP) dose preparation prior to administration and evaluated injection site reactions after dorsogluteal injection of PP once-every-6-months (PP6M) and once-every-3-months (PP3M) formulations from a double-blind (DB) noninferiority study. *Design and Methods*. Clinically stable patients receiving moderate/high doses of PP once-monthly (PP1M) (156 mg/mL; 234 mg/1.5 mL) or PP3M (546 mg/1.75 mL; 819 mg/2.63 mL) were randomly assigned 2:1 to corresponding dorsogluteal injections of PP6M (1092 mg/3.5 mL; 1560 mg/5 mL) or PP3M (546 mg/1.75 mL; 819 mg/2.63 mL) during a 12-month DB phase. Patients receiving PP6M injections received alternating matching placebo injections every 3 months between active doses to maintain blinding. Prior to administration, each PP formulation was prepared per specific instructions to ensure complete resuspension of the medication. *Findings*. Of 895 PP6M injections, one of two incomplete injections was possibly related to insufficient shaking before administration; neither resulted in an adverse reaction. After dorsogluteal administration, 59 of 478 patients who received PP6M (12.3%) and 11 of 224 patients who received PP3M (4.9%) reported an injection site–related treatment-emergent adverse event (TEAE), with pain being the most commonly reported (7.7% and 4.0%, respectively). Patient-reported pain decreased from baseline to end point in both groups. During the DB phase, injection site-related TEAEs associated with PP6M injections up to 5 mL and PP3M injections up to 2.63 mL were mild to moderate in severity; none were reported as serious, resulted in treatment discontinuation, or required dermatological consultation. *Practice Implications*. These results inform provider and patient expectations of PP6M administration and reinforce the importance of proper PP dose preparation and administration; future work could assess safety data from real-world clinical practice. This trial is registered with NCT03345342.

1. Introduction

Long-acting injectable antipsychotics (LAIs) offer several advantages over oral antipsychotic medications for adults diagnosed with schizophrenia, including a reduced need for daily oral medication, allowing patients to focus on their treatment plan and personal goals rather than their medication [1, 2]. In comparison with oral antipsychotics, LAIs offer more consistent plasma levels [1], have shown a delayed time to relapse [1–3] with the potential to reduce hospitalizations [4], and provide clearer attribution that the cause of relapse is not due to nonadherence [1–3, 5].

Recent clinical guidance supports the use of LAIs in adults with schizophrenia [6–8]. The National Council for Mental Wellbeing lists several recommended practices for prescribers, including initiating a discussion about LAIs in adult patients earlier after schizophrenia diagnosis [6]. In addition, the American Psychiatric Association

recommends that LAIs be considered for adult patients with schizophrenia if they prefer such treatment or if they have a history of poor or uncertain adherence [7]. Medicaid best practice guidelines for the state of Florida recommend initial treatment for schizophrenia with oral antipsychotics alone or oral antipsychotic followed by the same LAI [8]. Despite this clinical guidance and evidence supporting LAI use, these formulations are often underutilized in adult patients with schizophrenia [9, 10]. Several barriers and misconceptions may contribute to LAI underutilization. Clinicians may be unfamiliar with LAIs, have limited experience in administering LAI injections, or may be reluctant to discuss or recommend transitioning patients to an LAI antipsychotic medication if they are clinically stable on current therapy [11]. Patients may lack awareness of LAI treatment options or have logistical challenges in traveling to appointments for injections [7]. Misconceptions or concerns about side effects, fear of injections, and the stigma that LAIs are a last resort or punishment [9] may also be a deterrent for some patients and their caregivers.

Unlike oral antipsychotic medications, LAIs may be associated with a range of potential injection site reactions such as injection site pain, induration, redness, and tenderness [12]; however, these adverse events (AEs) are typically mild in severity. The frequency of injection site reactions and pain after administration of LAIs can be influenced by several factors, including the type of vehicle used (oil vs. aqueous based), injection volume, the site of injection, dose preparation and administration technique, and patient history with LAIs [12].

Paliperidone palmitate (PP) LAIs have been shown to be effective in delaying time to relapse in patients with schizophrenia [13–16]. In addition to PP once-monthly (PP1M) [17] and PP once-every-3-months (PP3M) [18] formulations, a PP once-every-6-months (PP6M) formulation was approved by the US Food and Drug Administration in 2021 for the treatment of adults with schizophrenia who have been adequately treated with PP1M for ≥4 months (with the last two doses being the same) or who have received PP3M for at least one 3-month cycle [19].

Given the differences in formulation, injection volume (PP6M, 3.5 or 5 mL; PP3M, up to 2.63 mL; PP1M, up to 1.5 mL), and injection site of each PP LAI product, we herein review the importance of proper PP dose preparation and administration and evaluate injection site reaction data from patients who received dorsogluteal injections of PP6M and PP3M during a 12-month, double-blind (DB) noninferiority study [16].

2. Materials and Methods

2.1. Paliperidone Palmitate Dose Preparation and Administration. To reduce the likelihood of an incomplete injection, each PP formulation has specific preparation and administration requirements to ensure complete resuspension of the medication. An overview of the steps to prepare PP1M, PP3M, and PP6M for injection is shown in Figure 1 [17–19]. With proper dose preparation and administration, PP6M doses of 1092 mg and 1560 mg result in PP total exposure ranges that are within the exposure range for corresponding doses of PP1M injections (156 mg and 234 mg, respectively) and PP3M injections (546 mg and 819 mg, respectively) (Figure 2) [17–19].

2.2. Injection Site Reaction Evaluation for PP6M and PP3M

2.2.1. Study Design. This was a post hoc analysis of data from the 12-month DB phase of a randomized, active-controlled, multicenter, noninferiority study (NCT03345342) (Figure 3) [16]. The study had three phases: a 28-day screening phase, an open-label (OL) maintenance phase (duration of 1 to 3 months depending on treatment received (one injection cycle of PP1M or PP3M)), and a 12-month DB phase. Patients who entered the study on an oral antipsychotic, injectable risperidone microspheres, or PP1M previously initiated but not stabilized at study entry were eligible to participate in an OL transition phase just prior to the OL maintenance phase to initiate and/or continue treatment with PP1M for up to 4 months. Following the maintenance phase, clinically stable patients treated with moderate or high doses of PP1M (156 or 234 mg) or PP3M (546 or 819 mg) were randomly assigned 2:1 to corresponding dorsogluteal injections of PP6M (1092 mg, $n = 230$; 1560 mg, $n = 248$) or PP3M (546 mg, $n = 106$; 819 mg, $n = 118$) during a 12-month DB phase. Patients randomly assigned to PP6M received matched placebo injections (20% Intralipid®) every 3 months between active doses to maintain blinding.

Prior to study initiation, injection personnel were trained in the proper preparation and administration of PP and placebo injections. Because PP6M is a highly concentrated product, it requires additional shaking for resuspension compared to PP1M or PP3M [19]. To resuspend PP6M, the syringe should be held with the tip cap up and shaken very fast in an up-and-down motion with a loose wrist for at least 15 seconds, followed by a brief rest, and then shaken for an additional 15 seconds. If 5 minutes pass before injection, the syringe should be shaken very quickly with the tip cap pointing up again for at least 30 seconds. When properly resuspended, the PP6M suspension will appear uniform and milky white, with no solid product on the sides and top of the syringe [19]. For administration, only the needle provided in the kit (1.5-inch, 20 gauge) should be used. The needle should be attached to the PP6M syringe, and a single injection should be administered deep into the upper-outer quadrant of the gluteal muscle [19]. Slow, firm, consistent pressure should be used to press the plunger down completely (approximately 30 seconds total).

2.2.2. Assessments. Treatment-emergent adverse events (TEAEs) were voluntarily reported by patients or obtained via interview in a nondirected manner at study visits. Injection site-related TEAEs for the PP6M group included TEAEs related to both PP6M and matched placebo injections.

Investigators evaluated the injection sites for erythema/redness, induration/swelling, and tenderness within 30 minutes after each injection using a four-

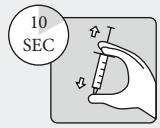
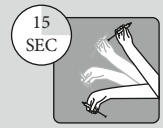
		PP1M	PP3M	PP6M
Single-Dose Prefilled Syringe Shaking Instructions			 Requires longer and more vigorous shaking with a loose wrist, with syringe tip cap pointed up	 Requires two 15-second periods of vigorous shaking with a loose wrist, with syringe tip cap pointed up
Dosing Interval		**Once Monthly**	Once Every 3 Months	Once Every 6 Months
Dose		39-234 mg[a]	273-819 mg[b]	1092 or 1560 mg[c]
Injection Site[d]		Deltoid or gluteal muscle (2 initiation doses in deltoid)	Deltoid or gluteal muscle	**Gluteal muscle only**
Needle Size Must be administered using only the needles that are provided in the kit	For adult patients who weigh <90 kg	**Deltoid**: 1-in, 23-gauge needle **Gluteal**: 1.5-in, 22-gauge needle	**Deltoid**: 1-in, 22-gauge needle **Gluteal**: 1.5-in, 22-gauge needle	1.5-in, 20-gauge needle
	For adult patients who weigh ≥90 kg	**Deltoid**: 1.5-in, 22-gauge needle **Gluteal**: 1.5-in, 22-gauge needle	**Deltoid**: 1.5-in, 22-gauge needle **Gluteal**: 1.5-in, 22-gauge needle	

Figure 1: Dose preparation for paliperidone palmitate formulations [17–19]. *Note*. PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months. [a]Following tolerability testing, the recommended initiation of PP1M is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. After the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle. The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39, 78, 156, and 234 mg). [b]Initiate PP3M after patients have been adequately treated with PP1M for at least 4 months, with the last 2 doses being the same. When the next PP1M dose is scheduled, administer a PP3M dose based on the previous 1-month injection dose using the equivalent 3.5-fold-higher dose. [c]Initiate PP6M only after adequate treatment has been established with either PP1M for at least 4 months, with the last 2 doses being the same, or PP3M for at least one 3-month injection cycle. The recommended initial PP6M dose is based on the previous PP1M dose or PP3M dose. If the last dose was PP1M 156 mg or PP3M 546 mg, the initial dose of PP6M should be 1092 mg. If the last dose was PP1M 234 mg or PP3M 819 mg, the initial dose of PP6M should be 1560 mg. [d]PP should be administered by a healthcare professional as a single injection. The dose should not be divided into multiple injections. Please refer to the full prescribing information, including boxed warning, of each formulation for complete dosing and administration information.

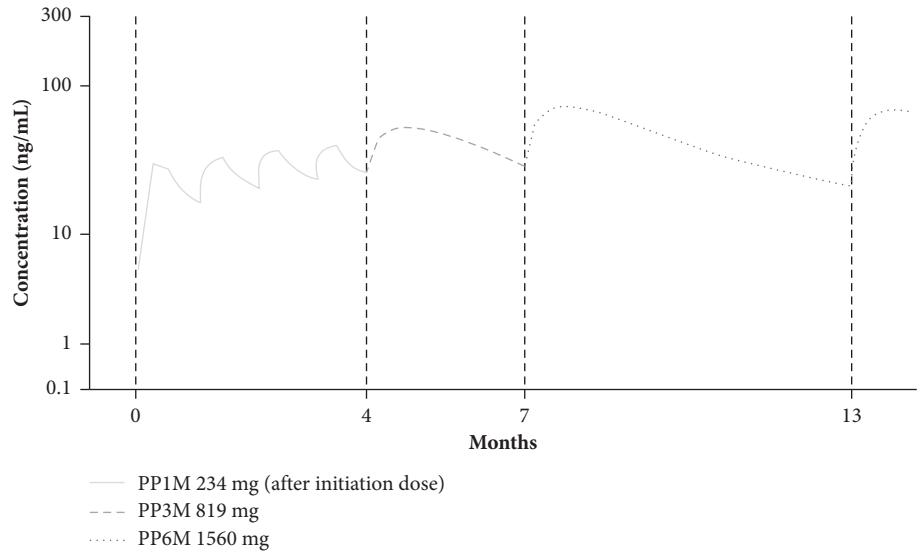


Figure 2: Plasma concentrations of PP formulations [17–19]. *Note*. PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months. Plasma concentrations represent deltoid injections for PP1M and PP3M. PP6M must be injected into the gluteal muscle only; it should not be administered by any other route [17–19]. Because of the difference in median pharmacokinetic profiles among PP1M, PP3M, and PP6M, caution should be exercised when making a direct comparison of their pharmacokinetic properties; correlation to clinical effect has not been established.

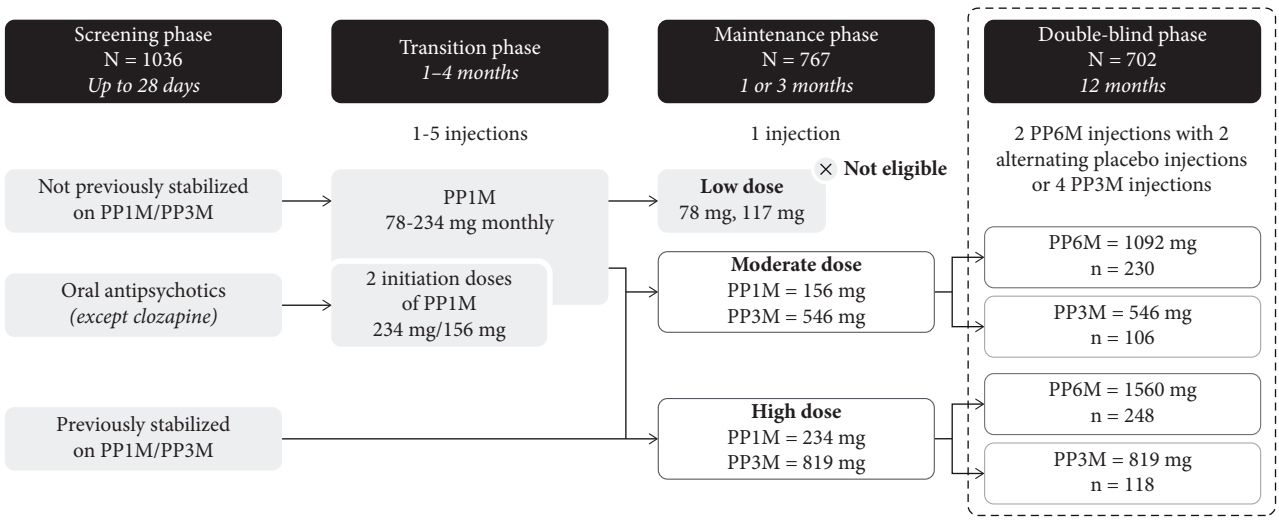


Figure 3: Study design. *Note.* PP1M, paliperidone palmitate once-monthly; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months.

category approach (0 = absent, 1 = mild, 2 = moderate, or 3 = severe). Injection site pain was evaluated using a patient-rated 100 mm visual analog scale (VAS). The VAS was presented as a 100 mm horizontal line on which the patient's pain intensity is represented by a point between "no pain at all" (0) to "unbearably painful" (100).

2.2.3. Statistical Methods. The safety analysis set (all randomly assigned patients who received at least one dose of DB study medication) was used to analyze data during the DB phase. TEAEs, VAS scores, and injection site reactions were summarized using descriptive statistics. No comparative statistical analyses were conducted.

2.2.4. Ethics. The study protocol and amendments were approved by an independent ethics committee or institutional review board. The trial was conducted in compliance with the ethical principles of the Declaration of Helsinki, good clinical practices, and applicable regulatory requirements. All patients provided written informed consent before study participation.

3. Results

3.1. Analysis of PP3M and PP6M Injection Site Reactions

3.1.1. Baseline Demographics and Disease Characteristics. In the DB phase of the study, a total of 702 clinically stabilized patients were randomly assigned in a 2:1 ratio to receive PP6M ($n = 478$) or PP3M ($n = 224$) (Table 1). In both treatment groups, the mean age of patients at baseline was approximately 40 years. Most patients were male (68.2%–68.8%), White (73.8%–75.0%), and not Hispanic or Latino (83.1%–87.9%). The mean age at the first diagnosis of schizophrenia was approximately 27 years.

3.1.2. Incomplete Injections. Of the 895 active injections administered within the PP6M group, two instances (0.2%) of incomplete injections were reported; both occurred in patients who received PP6M 1560 mg (5 mL suspension). Both instances were related to increased resistance within the syringe during injection; neither resulted in an adverse event. One instance was possibly related to insufficient shaking before administration, highlighting the need for proper dose preparation.

3.1.3. Injection Site-Related Treatment-Emergent Adverse Events. In the DB phase of the study, injection site-related TEAEs were reported in 59 of 478 patients (12.3%) in the PP6M group and 11 of 224 patients (4.9%) in the PP3M group. Injection site pain was the most commonly reported TEAE in both treatment groups (PP6M: 37 patients (7.7%); PP3M: 9 patients (4.0%) (Figure 4). All other injection site-related TEAEs, including induration, redness, and swelling, occurred in <2% of patients in both treatment groups. None of the injection site-related TEAEs were reported as serious, resulted in treatment discontinuation, or required dermatological consultation.

3.1.4. Investigator Evaluation of Injection Sites. The percentage of patients with injection site reactions, as determined by the investigator, is shown in Table 2. At both DB baseline and endpoint, erythema/redness, induration/swelling, and tenderness were primarily absent in both treatment groups (88.9%–99.8%) and were similar at high and moderate doses. No patients had severe reactions.

3.1.5. Injection Site-Related Pain. Overall, mean (SD) patient-rated VAS scores for injection site pain decreased from DB baseline to end point for patients in the PP6M group (17.22 (20.86)) to 5.41 (10.76)) and the PP3M group (14.98 (18.98) to 4.54 (8.93)). Changes from baseline were generally consistent across treatment groups and moderate

Table 1: Baseline demographics and disease characteristics in the double-blind intention-to-treat analysis set [16].

Characteristic	PP6M, $n = 478$	PP3M, $n = 224$
Mean age (SD), years	41.2 (11.77)	40.0 (10.98)
Sex, *n* (%)		
Male	326 (68.2)	154 (68.8)
Race, *n* (%)		
White	353 (73.8)	168 (75.0)
Asian	66 (13.8)	30 (13.4)
Black and/or African American	49 (10.3)	23 (10.3)
Other[a]	6 (1.3)	2 (0.9)
Ethnicity, *n* (%)		
Not Hispanic or Latino	397 (83.1)	197 (87.9)
Hispanic or Latino	75 (15.7)	25 (11.2)
Unknown	6 (1.3)	2 (0.9)
Mean baseline weight (SD), kg[b]	81.9 (16.86)	80.8 (17.01)
Mean baseline BMI (SD), kg/m^{2}[b]	27.9 (4.96)	27.5 (4.96)
Mean age at first diagnosis of schizophrenia (SD), years	27.7 (9.01)	27.5 (9.05)

Note. BMI, body mass index; PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months. [a]Includes patients who self-identified as Native Hawaiian or other Pacific Islander and as multiple races. [b]Based on open-label data.

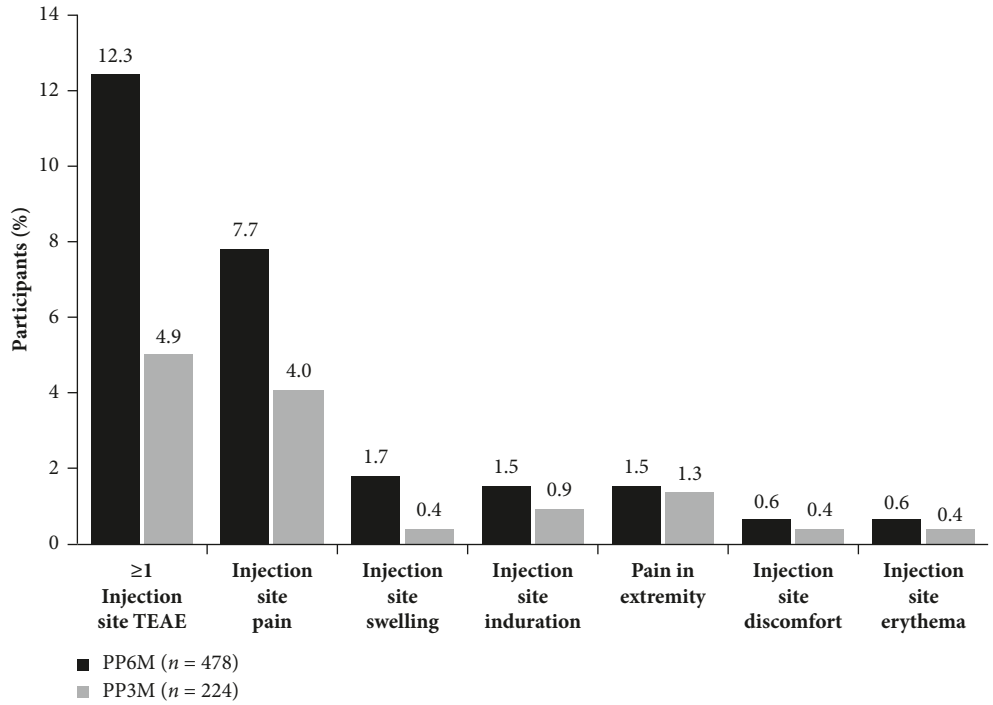


Figure 4: Injection site–related treatment-emergent adverse events during the double-blind phase. *Note*. PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months; TEAE, treatment-emergent adverse event.

and high doses (Figure 5). The mean patient-rated VAS scores for PP6M placebo injections given at months 3 and 9 were similar to those for active PP6M 1092 mg and 1560 mg injections at other timepoints (Figure 5).

4. Discussion

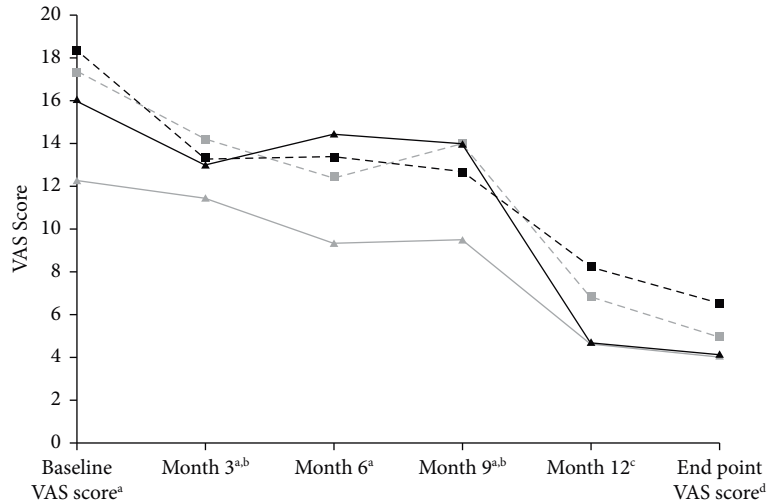
Administration of first-generation oil-based formulations of LAI antipsychotics, such as fluphenazine decanoate and haloperidol decanoate, is associated with significant injection site reactions and pain [20]. Repeated large-volume administrations of these oil-based LAI formulations are shown to cause muscle granuloma, fibrosis, and accumulation of oil in some patients [21], which may contribute to poor treatment adherence and thus, medication discontinuation and symptomatic relapse [22]. To prevent leakage from injection sites and reduce the incidence of injection site adverse effects associated with oil-based LAI antipsychotics, the Z-track technique is often recommended [12].

Newer generation LAI antipsychotics, including all available PP formulations (PP1M, PP3M, and PP6M), have minimal injection site pain, possibly because they are aqueous-based suspensions [23, 24] and do not require a Z-track injection technique. Proper dose preparation is

Table 2: Investigator evaluation of injection sites during the double-blind phase.

Patients, *n* (%)	PP6M						PP3M					
	Baseline, *n* = 478			End point, *n* = 477			Baseline, *n* = 224			End point, *n* = 223		
	Total	High dose	Moderate dose	Total	High dose	Moderate dose	Total	High dose	Moderate dose	Total	High dose	Moderate dose
Erythema/redness												
N	478	248	230	477	248	229	224	118	106	223	118	105
Absent	473 (99.0)	245 (98.8)	228 (99.1)	476 (99.8)	247 (99.6)	229 (100)	222 (99.1)	117 (99.2)	105 (99.1)	222 (99.6)	117 (99.2)	105 (100)
Mild	5 (1.0)	3 (1.2)	2 (0.9)	1 (0.2)	1 (0.4)	0	2 (0.9)	1 (0.8)	1 (0.9)	1 (0.4)	1 (0.8)	0
Induration/swelling												
n	478	248	230	477	248	229	224	118	106	223	118	105
Absent	469 (98.1)	242 (97.6)	227 (98.7)	475 (99.6)	247 (99.6)	228 (99.6)	220 (98.2)	116 (98.3)	104 (98.1)	222 (99.6)	117 (99.2)	105 (100)
Mild	9 (1.9)	6 (2.4)	3 (1.3)	2 (0.4)	1 (0.4)	1 (0.4)	4 (1.8)	2 (1.7)	2 (1.9)	1 (0.4)	1 (0.8)	0
Tenderness												
n	478	248	230	477	248	229	224	118	106	223	118	105
Absent	425 (88.9)	218 (87.9)	207 (90.0)	474 (99.4)	246 (99.2)	228 (99.6)	207 (92.4)	111 (94.1)	96 (90.6)	221 (99.1)	117 (99.2)	104 (99.0)
Mild	48 (10.0)	28 (11.3)	20 (8.7)	3 (0.6)	2 (0.8)	1 (0.4)	16 (7.1)	6 (5.1)	10 (9.4)	2 (0.9)	1 (0.8)	1 (1.0)
Moderate	5 (1.0)	2 (0.8)	3 (1.3)	—	—	—	1 (0.4)	1 (0.8)	0	—	—	—

Note. PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months.



PP6M 1560 mg (*n*)	248	233	218	207	81	248
PP6M 1092 mg (*n*)	230	220	205	193	70	229
PP3M 819 mg (*n*)	118	118	111	105	43	118
PP3M 546 mg (*n*)	106	97	93	88	29	105

Figure 5: Mean visual analog scale scores for injection site pain by PP3M and PP6M doses. *Note*. PP3M, paliperidone palmitate once-every-3-months; PP6M, paliperidone palmitate once-every-6-months; VAS, visual analog scale. The VAS scale ranged from 0 (no pain at all) to 100 (unbearably painful). [a]VAS assessed within 30 minutes of injection. [b]For PP6M doses, placebo injections were given at months 3 and 9 to maintain double-blinding. [c]VAS residual. [d]VAS residual/LOCF.

required for complete resuspension of the medication and to reduce the risk of an incomplete injection that could lead to patients not experiencing a full therapeutic response. Patient education can improve patient perceptions and assist in diminishing fears around the LAI injection experience. The consistent release of PP with sustained plasma concentrations over the various treatment frequencies and potential injection TEAEs should be explained to patients prior to PP administration. Regardless of LAI dosing frequency and administration, all patients should maintain regular follow-up appointments as deemed clinically necessary by the prescriber and the extended treatment team.

Unlike PP1M and PP3M, which may be injected into deltoid or gluteal muscles, PP6M can only be injected into gluteal muscle [19]. According to the prescribing information [19], PP6M should be injected into the upper-outer quadrant of the gluteal muscle, with future injections alternated between the two gluteal muscles [19]. In the present study, PP6M and PP3M were both administered in the dorsogluteal region to maintain treatment blinding [16]. The dorsogluteal site may be preferred by patients compared with the ventrogluteal site, given that it is more easily accessed by healthcare providers and less embarrassing for the patient.

The findings of this post hoc analysis regarding injection site reactions are consistent with those observed across PPLAI formulations [13–15]. Results from the present post hoc analysis showed that injection site-related TEAEs associated with PP6M and PP3M administration occurred in 12.3% and 4.9% of patients, respectively, and none were reported as serious, resulted in treatment discontinuation, or required dermatological consultations. Injection site pain was the most commonly reported TEAE in both treatment groups. In the present study, mean VAS scores were comparable between both PP6M and PP3M treatment groups at baseline and decreased over time in both moderate- and high-dose groups. Mean VAS scores for PP6M placebo injections given at months 3 and 9 were similar to VAS scores for active PP6M 1092 mg and 1560 mg injections given at other timepoints. A decrease in VAS scores over the course of multiple injections has been observed in other studies investigating LAI injection site pain [25, 26] and has been attributed to patients becoming acclimated to PP injections as they become more experienced with receiving injections.

Several limitations should be considered when interpreting these findings. First, this post hoc analysis was limited to the DB phase of the noninferiority study and does not capture injection site reactions that occurred in the transition and maintenance phases. Second, patients who were exposed to PP or another LAI for an extended period before study initiation could have described injection site reactions and pain differently than patients who were naive to treatment with LAIs. Lastly, patients in the PP6M group received placebo injections every 3 months between active doses. Consequently, mean VAS scores are calculated based on data from both PP and placebo injections, which may have impacted injection site-related outcomes.

5. Conclusion

In conclusion, proper dose preparation and administration can help reduce the risk of an incomplete PP injection. Injection site-related TEAEs were reported in 12.3% of patients who received PP6M during the DB phase of a noninferiority study; none were reported as serious, resulted in treatment discontinuation, or required dermatological consultation. Incidence and type of injection site-related reactions associated with PP6M were similar regardless of dose (1092 mg and 1560 mg) and decreased throughout the duration of the study, demonstrating that larger injection volumes of LAIs (up to 5 mL) can be well tolerated when proper preparation and administration steps are followed. These results inform provider and patient expectations of PP6M administration along with the importance of proper PP dose preparation and administration; future work could assess safety data from real-world clinical practice. As new LAI formulations of antipsychotics are approved by the FDA, nursing and pharmacy guidelines, policies, and procedures should be updated to reflect how these medications are administered.

Data Availability

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at https://yoda.yale.edu.

Additional Points

Previous Presentations. College of Psychiatric and Neurologic Pharmacists (CPNP) Congress; April 24-27, 2022; San Antonio, Texas; The American Psychiatric Nurses Association (APNA) Congress; October 19-22, 2022; Long Beach, California.

Ethical Approval

The study protocol and amendments were approved by an independent ethics committee or institutional review board. The trial was conducted in compliance with the ethical principles of the Declaration of Helsinki, good clinical practices, and applicable regulatory requirements. All patients provided written informed consent before study participation.

Conflicts of Interest

KJ, DN, SF, SW, JKS, and OL are employees of Janssen Scientific Affairs, LLC, and stockholders of Johnson & Johnson. SK has received advisory board consulting fees and speakers' honoraria from Janssen Scientific Affairs, LLC.

Acknowledgments

Our dear friend and colleague, Dean Najarian, died on January 9, 2023. He dedicated his life to helping people with severe mental illness and will be deeply missed. Dean was instrumental in the design of this study and assisted with data interpretation and writing and review of early drafts of the manuscript. The authors thank Lynn Brown, PhD, and Soniya Patel, PhD (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by the Janssen Scientific Affairs, LLC, Titusville, NJ, USA.

References

[1] S. Brissos, M. R. Veguilla, D. Taylor, and V. Balanza-Martinez, "The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal," *Therapeutic Advances in Psychopharmacology*, vol. 4, no. 5, pp. 198–219, 2014.

[2] F. Pietrini, U. Albert, A. Ballerini et al., "The modern perspective for long-acting injectables antipsychotics in the patient-centered care of schizophrenia," *Neuropsychiatric Disease and Treatment*, vol. 15, pp. 1045–1060, 2019.

[3] M. H. Lafeuille, F. Laliberte-Auger, P. Lefebvre, C. Frois, J. Fastenau, and M. S. Duh, "Impact of atypical long-acting injectable versus oral antipsychotics on rehospitalization rates and emergency room visits among relapsed schizophrenia patients: a retrospective database analysis," *BMC Psychiatry*, vol. 13, no. 1, p. 221, 2013.

[4] T. Kishimoto, K. Hagi, S. Kurokawa, J. M. Kane, and C. U. Correll, "Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies," *The Lancet Psychiatry*, vol. 8, no. 5, pp. 387–404, 2021.

[5] J. M. Kane, S. Leucht, D. Carpenter, and J. P. Docherty, "The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary," *The Journal of Clinical Psychiatry*, vol. 64, no. 12, pp. 5–19, 2003.

[6] National Council for Mental Wellbeing, *Guide to Long-Acting Medications for Clinicians and Organizations*, National Council for Mental Wellbeing, Washington, DC, USA, 2022, https://www.thenationalcouncil.org/wp-content/uploads/2021/12/2022.02.02_NC_Updated-Guide-To-LAMs.pdf.

[7] American Psychiatric Association, *The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia*, American Psychiatric Association, Washington, DC, USA, 3rd edition, 2021.

[8] University of South Florida College of Behavioral and Community Sciences, *2019–2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults*, University of South Florida College of Behavioral and Community Sciences, Tampa, FL, USA, 2020, https://floridabhcenter.org/wp-content/uploads/2021/04/2019-Psychotherapeutic-Medication-Guidelines-for-Adults-with-References_06-04-20.pdf.

[9] C. U. Correll, L. Citrome, P. M. Haddad et al., "The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence," *The Journal of Clinical Psychiatry*, vol. 77, no. 3, pp. 1–24, 2016.

[10] J. C. West, S. C. Marcus, J. Wilk, L. M. Countis, D. A. Regier, and M. Olfson, "Use of depot antipsychotic medications for medication nonadherence in schizophrenia," *Schizophrenia Bulletin*, vol. 34, no. 5, pp. 995–1001, 2008.

[11] L. Citrome, E. Belcher, S. Stacy, M. Suett, M. Mychaskiw, and G. D. Salinas, "Management of schizophrenia with long-acting injectable antipsychotic medications: an assessment of the educational needs of clinicians," *Neuropsychiatric Disease and Treatment*, vol. 18, pp. 111–123, 2022.

[12] M. Zolezzi, R. Abouelhassan, Y. Eltorki, P. M. Haddad, and M. Noorizadeh, "Long-acting injectable antipsychotics: a systematic review of their non-systemic adverse effect profile," *Neuropsychiatric Disease and Treatment*, vol. 17, pp. 1917–1926, 2021.

[13] A. J. Savitz, H. Xu, S. Gopal et al., "Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study," *International Journal of Neuropsychopharmacology*, vol. 19, no. 7, Article ID pyw018, 2016.

[14] J. Berwaerts, Y. Liu, S. Gopal et al., "Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial," *JAMA Psychiatry*, vol. 72, no. 8, pp. 830–839, 2015.

[15] D. Hough, S. Gopal, U. Vijapurkar, P. Lim, M. Morozova, and M. Eerdekens, "Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study," *Schizophrenia Research*, vol. 116, no. 2-3, pp. 107–117, 2010.

[16] D. Najarian, P. Sanga, S. Wang et al., "A randomized, double-blind, multicenter, noninferiority study comparing paliperidone palmitate 6-month versus the 3-month long-acting injectable in patients with schizophrenia," *International Journal of Neuropsychopharmacology*, vol. 25, no. 3, pp. 238–251, 2021.

[17] Janssen Pharmaceuticals Inc, *INVEGA SUSTENNA® (Paliperidone Palmitate) [package Insert]*, Janssen Pharmaceuticals Inc, Titusville, NJ, USA, 01/2019.

[18] Janssen Pharmaceuticals Inc, *INVEGA TRINZA® (Paliperidone Palmitate) Extended-Release Injectable Suspension, for Intramuscular Use [prescribing Information]*, Janssen Pharmaceuticals, Inc, Titusville, NJ, USA, 2019.

[19] Janssen Pharmaceuticals Inc, *INVEGA HAFYERA™ (Paliperidone Palmitate) Extended-Release Injectable Suspension, for Gluteal Intramuscular Use [highlights of Prescribing Information]*, Janssen Pharmaceuticals, Inc, Titusville, NJ. USA, 2021.

[20] L. Citrome, "New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia," *Expert Review of Neurotherapeutics*, vol. 13, no. 7, pp. 767–783, 2013.

[21] J. Hay, "Complications at site of injection of depot neuroleptics," *BMJ*, vol. 311, no. 7002, p. 421, 1995.

[22] G. Kaplan, J. Casoy, and J. Zummo, "Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia," *Patient Preference and Adherence*, vol. 7, pp. 1171–1180, 2013.

[23] J. P. Lindenmayer, K. Jarboe, C. A. Bossie, Y. Zhu, A. Mehnert, and R. Lasser, "Minimal injection site pain and high patient satisfaction during treatment with long-acting risperidone," *International Clinical Psychopharmacology*, vol. 20, no. 4, pp. 213–221, 2005.

[24] S. M. Paquette, H. Dawit, M. B. Hickey, E. Merisko-Liversidge, O. Almarsson, and D. R. Deaver, "Long-acting atypical antipsychotics: characterization of the local tissue response," *Pharmaceutical Research*, vol. 31, no. 8, pp. 2065–2077, 2014.

[25] J. Kern Sliwa, A. Savitz, I. Nuamah et al., "An assessment of injection site reaction and injection site pain of 1-month and 3-month long-acting injectable formulations of paliperidone palmitate," *Perspectives in Psychiatric Care*, vol. 54, no. 4, pp. 530–538, 2018.

[26] E. Ting, S. Kamalvand, D. Shang, D. Siskind, and S. Kisely, "Does the frequency of administration of long acting injectable antipsychotics impact psychiatric outcomes and adverse effects: a systematic review and meta-analysis," *Journal of Psychiatric Research*, vol. 109, pp. 193–201, 2019.