Three-month Injectable Paliperidone Palmitate for the Treatment of Adults with Schizophrenia: A Review of Clinical Effectiveness, Safety, and Guidelines
**Authors:** Chuong Ho, Sarah Jones


**ISSN:** 1922-8147 (online)

**Disclaimer:** The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners’ own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada’s federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user’s own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian Copyright Act and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada’s health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada’s federal, provincial, and territorial governments, with the exception of Quebec.
Context and Policy Issues
The long-term injectable formulation paliperidone palmitate, a dopamine antagonist and 5-HT2A antagonist of the atypical antipsychotic class of medication has been used to treat schizophrenia,1-7 a mental disorder that affects 1% of the Canadian population.8 Once-monthly injectable (Invega Sustenna®) and 3-month injectable (Invega Trinza®) paliperidone palmitate formulations have been shown to have higher efficacy over placebo, and are generally well tolerated.9-15 Convenience with extended formulations of paliperidone palmitate like the 3-month injectable version may lead to an increase in medication adherence which is important in controlling symptoms, preventing relapses and re-hospitalizations. The comparative clinical effectiveness and safety of once-monthly and 3-month injectable paliperidone palmitate formulations are however not clear, and needs evidence from direct comparisons between the two formulations.

This Rapid Response report aims to review the clinical effectiveness and safety of 3-month injectable paliperidone palmitate (PP3M) for schizophrenia compared with once-monthly injectable formulation (PP1M) and placebo in the treatment of adults with schizophrenia. Evidence-based guidelines regarding the use of 3-month injectable paliperidone palmitate for the adults with schizophrenia will also be examined.

Research Questions
1. What is the clinical effectiveness and safety of 3-month injectable paliperidone palmitate for the treatment of adults with schizophrenia?

2. What are the evidence-based guidelines associated with the use of 3-month injectable paliperidone palmitate for the treatment of adults with schizophrenia?

Key Findings
Evidence from one randomized controlled trial showed that patients with schizophrenia randomly assigned to placebo were almost four times more likely to have a relapse compared to 3-month injectable paliperidone palmitate, and the 3-month formulation was generally tolerable. Findings from another randomized study showed that 3-month injectable paliperidone palmitate was not inferior to the once-monthly injectable formulation in preventing relapse in adults with schizophrenia during 48 weeks of treatment. Tolerability profiles were similar between the two formulations. Indirect comparison from a post hoc analysis showed that patients remained relapse free for approximately six and 13 months following discontinuation of once-monthly injectable paliperidone palmitate and the 3-month injectable formulation, respectively. There were no evidence-based guidelines found associated with the use of 3-month injectable paliperidone palmitate for the treatment of adults with schizophrenia.

Methods
A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search
was also limited to English language documents published between January 1, 2012 and August 2, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods
One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with schizophrenia (≥ 18 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>3-month paliperidone palmitate injectable formulation (Invega Trinza)</td>
</tr>
</tbody>
</table>
| Comparator       | Q1: once-monthly paliperidone palmitate injectable formulation (Invega Sustenna) Placebo  
|                  | Q2: No comparator |
| Outcomes         | Q1: Clinical effectiveness/efficacy and safety  
|                  | Q2: Guidelines |
| Study Designs     | Heath technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled trials, evidence-based guidelines |

Exclusion Criteria
Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications were already reported in the included SRs, or were published prior to 2012.

Critical Appraisal of Individual Studies

The included clinical studies were assessed using the Downs and Black checklist.\(^\text{\textsuperscript{16}}\)

Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available
A total of 403 citations were identified in the literature search. Following screening of titles and abstracts, 398 citations were excluded and five potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, four publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.
Summary of Study Characteristics
The literature search identified one clinical trial\(^{17}\) comparing the efficacy and safety of PP3M to placebo, and two clinical trials\(^{18,19}\) comparing the efficacy and safety of PP3M to PP1M in adult patients with schizophrenia.

The first randomized controlled trial (RCT)\(^{17}\) compared the efficacy and safety of PP3M to placebo in adult patients (18 to 70 years old) with schizophrenia. After screening for patients who met inclusion criteria and a 17-week open-label phase with PP1M, clinically stable patients, determined by symptoms scores measurements, entered the double-blind phase in which patients were randomized to PP3M or placebo for variable lengths of time (until relapse occurred, patients withdrew from the study, or the study was terminated). Primary outcomes were relapse rates during the double-blind phase; secondary outcomes were changes in symptom scores from double-blind baseline and adverse events. This study was conducted in eight countries from North America, South America, Europe and Asia.

The randomized, double-blind, non-inferiority study\(^{18}\) compared the efficacy and safety of PP3M to PP1M in adult patients (18 to 70 years old) with schizophrenia, previously stabilized on PP1M. After screening for patients who met inclusion criteria and a 17-week open-label phase with PP1M, clinically stable patients, determined by symptoms scores measurements, entered the double-blind phase in which patients were randomized to PP1M or PP3M for 48 weeks (matched placebo injections were used monthly in the PP3M group). Primary outcomes were relapse rates during the double-blind phase; secondary outcomes were changes in symptom scores from double-blind baseline and adverse events. The trial was conducted in 26 countries from North America, South America, Australia, Europe and Asia.

The post hoc analysis\(^{19}\) analyzed data from three separate randomized, double-blind trials that individually compared oral paliperidone, PP1M and PP3M to placebo, and performed indirect comparisons between PP1M and PP3M. Outcomes were relapse rates following discontinuing medication. The study was conducted in the US.

Characteristics of the included studies are detailed in Appendix 2.

Summary of Critical Appraisal
The included studies\(^{17-19}\) had clearly described hypotheses, method of selection from source population and representation of the study population, main outcomes, interventions, patient characteristics, and main findings. Estimates of random variability and actual probability values were provided. One RCT\(^{18}\) was a non-inferiority study which determined the non-inferiority margin based on published literature composed of historical placebo-controlled trials on PP1M; this determination may have been undermined by the assumption that the active control in the current study of PP3M is similar to the effect of PP1M in the historical cohort. Patients entering the double-blind phase of both RCTs\(^{17,18}\) were already shown to be responsive and tolerable to PP1M; this may increase the treatment effect of the intervention and limit the conclusion of the study to the population of patients who were already responsive to PP1M. The post hoc analysis\(^{19}\) analysed data from three separate studies which had similar patients characteristics but different medication dosages, treatment periods, and follow-up times which may affect the precision of the findings. The comparison between formulations was indirect with sound methodology,
and it was unclear whether study had sufficient power to detect a clinically important effect, as no power calculation was reported.

Details of the critical appraisal of the included studies are presented in Appendix 3.

Summary of Findings
The main findings of the included studies are presented in Appendix 4.

*What is the clinical effectiveness and safety of 3-month paliperidone palmitate injectable formulation for the treatment of adults with schizophrenia?*

The randomized, double-blind study\(^{17}\) compared the efficacy and safety of PP3M to placebo in adult patients with schizophrenia, previously stabilized on PP1M. After screening and a 17-week open-label phase with PP1M, clinically stable patients entered the double-blind phase in which patients were randomized to PP1M or placebo for varied lengths of time (until relapse occurred, patients withdrew from the study, or the study was terminated). Treatment with PP3M significantly delayed time to first relapse compared to placebo; patients randomly assigned to placebo were almost four times more likely to have relapse during the double-blind phase compared to those assigned to PP3M. PP3M was generally tolerable; headache, weight increase, nasopharyngitis and akathisia were the most common treatment emergent adverse events (TEAEs) that were more frequent in the PP3M group than in the placebo group. Serious TEAEs occurred three times more often in patients with placebo than those with PP3M, mostly related to increase in psychiatric symptoms.

The randomized, double-blind, non-inferiority study\(^{18}\) compared the efficacy and safety of PP3M to PP1M in adult patients with schizophrenia, previously stabilized on PP1M. After screening and a 17-week open-label phase with PP1M, clinically stable patients entered the double-blind phase in which patients were randomized to PP1M or PP3M for 48 weeks. Non-inferiority of PP3M would be concluded if the lower limit of the 2-sided 95% CI of the difference in relapse-free rates between the two formulations was larger than the pre specified margin -15%. The relapse rates were similar in both groups, 8% in PP3M group and 9% in PP1M group. The lower bound of the 95% CI between the two formulations in the percentage of patients who remained relapse-free (-2.7%) was found to be larger than the pre-specified non-inferiority margin. There was no significant difference from double-blind baseline between the two formulations in schizophrenia symptom scores. Both formulations lead to similar tolerability profiles, with most common adverse events being increased weight, nasopharyngitis, anxiety and headache. The authors concluded that PP3M was non-inferior to PP1M in the treatment of adults with schizophrenia.

The post hoc analysis\(^{19}\) analysed data from three separate randomized, double-blind trials that individually compared oral paliperidone, PP1M and PP3M to placebo. Post hoc analysis showed that following discontinuing medication, about 50% of patients remained relapse-free for approximately two months for oral paliperidone, six months for PP1M and 13 months for PP3M. The authors concluded that among the three formulations, PP3M provided the most substantial delay in time to relapse after medication discontinuation.
What are the evidence-based guidelines associated with the use of 3-month paliperidone palmitate injectable formulation for the treatment of adults with schizophrenia?

There was no evidence found in evidence-based guidelines regarding the use of the 3-month paliperidone palmitate injectable formulation for the treatment of adults with schizophrenia.

Limitations
The comparative evidence between PP3M and PP1M is from a non-inferiority study and indirect comparisons from a post hoc analysis. The efficacy and safety of PP3M were determined in patients who were already shown to be responsive and tolerable to paliperidone palmitate; the findings are not generalizable to a treatment naïve population.

Conclusions and Implications for Decision or Policy Making

Evidence from one RCT showed that patients with schizophrenia randomly assigned to placebo were almost four times more likely to have a relapse compared to 3-month paliperidone palmitate, and the 3-month formulation was generally tolerable. Evidence from one RCT showed that the 3-month paliperidone palmitate injectable formulation was not inferior to once-monthly formulation in preventing relapse in adults with schizophrenia during a 48 weeks treatment in patients who were already stable with once-monthly medication. Tolerability profiles were similar between the two formulations. Indirect comparison from a post hoc analysis between the two formulations showed that patients remained relapse free for longer period of times following medication discontinuation with 3-month formulation than oral and once-monthly formulations.

In agreement with the current evidence that PP3M is not inferior to PP1M in patients who were already successfully treated with PP1M, a practical guidance commentary has suggested that patients can be switched safely from PP1M to PP3M and the PP3M product should be used without prior treatment with PP1M, but rather as a maintenance therapy for patients who have already demonstrated a therapeutic effect and tolerability to PP1M.20

Even though the superiority of PP3M over PP1M has not been demonstrated by direct comparison, the findings of non-inferiority suggest the possibility to reduce the dosing interval of antipsychotics to four times a year, thus potentially increasing patients’ adherence to treatment. A recent survey of patients and physicians on hypothetical antipsychotic profiles defined by efficacy, safety, and mode of administration found that both respondents preferred once-monthly injectable formulations over oral daily products, with physicians showing greater preference for 3-month over 1-month.21 Caregiver burden may also be improved following transition from daily oral product to paliperidone palmitate long-acting injectable formulations, especially in urging, worrying, tension and supervision domains.22

More evidence from large RCTs is needed to formulate guidelines on the use of PP3M in the treatment of patients with schizophrenia.
REFERENCES


Appendix 1: Selection of Included Studies

403 citations identified from electronic literature search and screened

398 citations excluded

5 potentially relevant articles retrieved for scrutiny (full text, if available)

2 potentially relevant reports retrieved from other sources (grey literature, hand search)

7 potentially relevant reports

4 reports excluded:
- irrelevant outcomes (2)
- reviews (2)

3 reports included in review
### Appendix 2: Characteristics of Included Publications

#### Table A1: Characteristics of Included Clinical Studies

<table>
<thead>
<tr>
<th>First Author, Year, Country</th>
<th>Study Design Study Objectives</th>
<th>Interventions/Compartmenters</th>
<th>Patients</th>
<th>Main Outcomes</th>
</tr>
</thead>
</table>
| Berwaerts, 2015, 8 countries from North and South America, Europe, Asia | Randomized controlled trial  
“To evaluate the efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo in delaying time to relapse of schizophrenia symptoms” (p 830) | Paliperidone palmitate 3-month formulation  
Placebo | Screening phase (620 patients; oral paliperidone for < 3 weeks)  
Open label phase (506 patients; PP1M for 17 weeks)  
Double-blind phase (305 clinically stable patients; 270 patients analysed; PP3M or placebo for variable times)  
Patients mean age: 37.8 (SD 11.01) | Primary outcome: time to first relapse during double-blind phase  
Secondary outcomes:  
Positive and negative symptom score (PANSS)  
Clinical Global Impression-Severity Score (CGI-S score)  
Personal and Social Performance score (PSP score)  
Tolerability (adverse events) |
| Savitz, 2016, 26 countries from North America, South America, Australia, Europe, Asia | Randomized controlled, double-blind non-inferiority trial  
“The current study was designed to demonstrate that the efficacy of PP3M in treating the symptoms of schizophrenia in patients stabilized on PP1M was not less effective (noninferior) than PP1M in these patients” (p 2) | Paliperidone palmitate 3-month formulation  
Paliperidone palmitate 1-month formulation | Screening phase (1716 patients; oral paliperidone for 4 to 6 days)  
Open label phase (1429 patients; PP1M for 17 weeks)  
Double-blind phase (1016 clinically stable patients; 948 patients analysed; PP1M or PP3M for 48 weeks)  
Patients mean age: 38.7 (SD 12.08) | Primary outcome: Relapse rate during double-blind phase  
Secondary outcomes:  
Positive and negative symptom score (PANSS)  
Clinical Global Impression-Severity Score (CGI-S score)  
Personal and Social Performance score (PSP score)  
Tolerability (adverse events) |
| Weiden, 2017, US | Post Hoc Analysis (data from 3 double-blind, placebo-controlled RCTs)  
To evaluate the effect of oral paliperidone, once-monthly and 3-month paliperidone palmitate formulations on time to relapse following medication discontinuation | Once-daily oral paliperidone  
Once-monthly paliperidone palmitate  
3-month paliperidone palmitate | 101 patients withdrawn from oral paliperidone  
203 patients withdrawn from PP1M  
145 patients withdrawn from PP3M  
Patients mean age: 37.5 to 39.4 years | Relapse rate during medication discontinuation  
Relapse risk |

PP1M = Once-monthly paliperidone palmitate; PP3M = 3-month paliperidone palmitate; SD = standard deviation.
### Appendix 3: Critical Appraisal of Included Publications

#### Table A2: Summary of Critical Appraisal of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical appraisal of included clinical trials (Downs and Black[16])</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Berwaerts[17] | • randomized, double-blind controlled trial  
• hypothesis clearly described  
• method of selection from source population and representation described  
• loss to follow-up reported  
• main outcomes, interventions, patient characteristics, and main findings clearly described  
• estimates of random variability and actual probability values provided  
• study had sufficient power to detect a clinically important effect | • patients entering the double-blind phase were already shown to be responsive and tolerable to paliperidone; this may increase the treatment effect of the intervention. |
| Savitz[18] | • randomized, double-blind controlled trial  
• hypothesis clearly described  
• method of selection from source population and representation described  
• loss to follow-up reported  
• main outcomes, interventions, patient characteristics, and main findings clearly described  
• estimates of random variability and actual probability values provided  
• study had sufficient power to detect a clinically important effect | • pre-specified non-inferiority margin was based on historical placebo-controlled trials on once-monthly formulation.  
• patients entering the double-blind phase were already shown to be responsive and tolerable to paliperidone; this may increase the treatment effect of the intervention. |
| Weiden[19] | • Post hoc analysis  
• hypothesis clearly described  
• method of selection from source population and representation described  
• loss to follow-up reported  
• main outcomes, interventions, patient characteristics, and main findings clearly described  
• estimates of random variability and actual probability values provided | • post hoc analysis of data from 3 separate studies which may have had different medication dosages, treatment periods, follow-up times  
• indirect comparison  
• unclear whether study had sufficient power to detect a clinically important effect. |
### Appendix 4: Main Study Findings and Author’s Conclusions

**Table A3: Main Study Findings and Authors’ Conclusions**

<table>
<thead>
<tr>
<th>Berwaerts<strong>17</strong></th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>“Compared with placebo, the 3-month formulation of paliperidone palmitate administered 4 times yearly significantly delayed time to relapse in patients with schizophrenia. The 3-month formulation was generally tolerable and has a safety profile consistent with other marketed paliperidone formulations.” (p 830)</td>
</tr>
<tr>
<td>Relapse rate (% of patients)</td>
<td></td>
</tr>
<tr>
<td>PP3M: 7%; placebo 23%</td>
<td></td>
</tr>
<tr>
<td>(independent data monitoring committee recommended early study termination due to efficacy)</td>
<td></td>
</tr>
<tr>
<td>PP3M vs placebo (hazard ratio; 95% CI): 3.45 (1.73 – 6.88) (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td><strong>Time to first relapse</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo 274 days; PP3M not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>PANSS (mean score, standard deviation)</td>
<td></td>
</tr>
<tr>
<td>PP3M 54.9 (9.95); placebo 54.2 (9.34) P values not reported</td>
<td></td>
</tr>
<tr>
<td>PANSS difference from double-blind baseline (mean change, standard deviation)</td>
<td></td>
</tr>
<tr>
<td>PP3M -0.5 (8.36); placebo 6.7 (14.40) P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>CGI-S (mean change, standard deviation)</td>
<td></td>
</tr>
<tr>
<td>PP3M 0.1 (0.60); placebo 0.4 (0.87) P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>PSP scores mean change, standard deviation</td>
<td></td>
</tr>
<tr>
<td>PP3M -0.5 (6.63); placebo -4.2 (9.70) P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Adverse events (TEAEs)</td>
<td></td>
</tr>
<tr>
<td>62% of PP3M patients; placebo 58% of patients had at least 1 TEAE.</td>
<td></td>
</tr>
<tr>
<td>Serious TEAEs: 3% in PP3M group; 10% in placebo group (related to increase in psychiatric symptoms)</td>
<td></td>
</tr>
<tr>
<td>TEAEs more frequent in PP3M group than placebo: headache (9% vs 4%), weight increase (9% vs 3%), nasopharyngitis (6% vs 1%), akathisia (4% vs 1%)</td>
<td></td>
</tr>
</tbody>
</table>

<p>| Savitz<strong>18</strong> | |
| Primary outcomes | |
| Relapse rate (% of patients) | |
| PP3M: 37/458 (8%) | |
| PP1M: 45/490 (9%) | |
| Most common reason for relapse: increase of ≥25% of total PANSS score and psychiatric hospitalizations. | |
| Relapse-free rate (based on Kaplan-Meier estimates) | |
| PP3M: 91.2% | |
| PP1M: 90.0% | |
| Difference: 1.2% (95% CI -2.7; 5.1) (pre-specified non-inferiority margin: -15%) | |
| “These results confirm the primary study hypothesis that the efficacy (determined by percentage of patients who remained relapse free) of PP3M is non inferior to that of PP1M” (p 13) | |</p>
<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>PANSS, CGI-S, PSP scores: differences in changes from double-blind baseline not statistically significant between treatments</td>
<td></td>
</tr>
<tr>
<td>Adverse events (TEAEs)</td>
<td></td>
</tr>
<tr>
<td>PP3M: 68%</td>
<td></td>
</tr>
<tr>
<td>PP1M: 66% (statistical significance not reported)</td>
<td></td>
</tr>
<tr>
<td>Most common TEAEs: increased weight, nasopharyngitis, anxiety, headache</td>
<td></td>
</tr>
<tr>
<td>More men in the PP1M group (45%) had high prolactin levels than in the PP3M group (39%)</td>
<td></td>
</tr>
<tr>
<td>Similar percentage of women in the PP1M group (32%) had high prolactin levels as in the PP3M group (33%)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>1 death in PP3M (liver cancer)</td>
<td></td>
</tr>
<tr>
<td>3 deaths in PP1M (1 each due to suicide attempt, self-inflicted toxicity to other agents, bacterial meningitis)</td>
<td></td>
</tr>
<tr>
<td><strong>Days to relapse (median days)</strong></td>
<td></td>
</tr>
<tr>
<td>Once-daily oral paliperidone: 58 days (95% CI 42 - 114)</td>
<td></td>
</tr>
<tr>
<td>PP1M: 172 days (95% CI 134 - 222)</td>
<td></td>
</tr>
<tr>
<td>PP3M: 395 days (95% CI 274 - not reached)</td>
<td></td>
</tr>
<tr>
<td><strong>Relapse risk</strong></td>
<td></td>
</tr>
<tr>
<td>56% lower for patients discontinuing PP1M than for those discontinuing oral paliperidone ($P &lt; 0.001$)</td>
<td></td>
</tr>
<tr>
<td>79% lower for patients discontinuing PP3M than for those discontinuing oral paliperidone ($P &lt; 0.001$)</td>
<td></td>
</tr>
<tr>
<td>52% lower for patients discontinuing PP3M than for those discontinuing PP1M ($P &lt; 0.001$)</td>
<td></td>
</tr>
<tr>
<td><strong>Weiden</strong></td>
<td></td>
</tr>
<tr>
<td>&quot;Of the 3 formulations evaluated, PP3M conferred the most enduring relapse prevention&quot; (p 67)</td>
<td></td>
</tr>
</tbody>
</table>

CGI-S = Clinical Global Impression-Severity Score; PANSS = Positive and negative symptom score; PP1M = 1-month paliperidone palmitate formulation; PP3M = 3-month paliperidone palmitate formulation; PSP = Personal and Social Performance score; TEAEs = treatment-emergent adverse events.